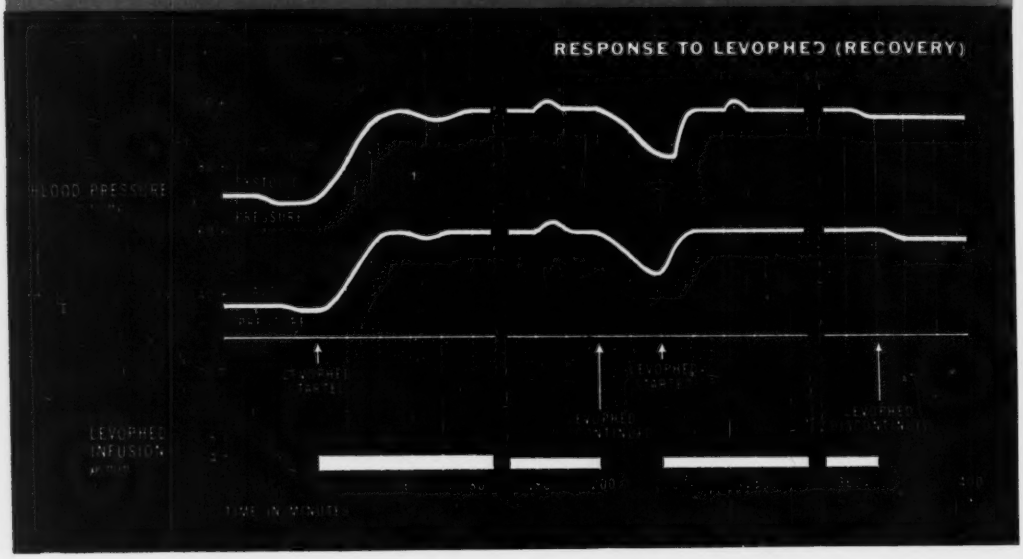
MARCH 1955
VOL. XI NO. 3

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Published by Grune & Stratton, Inc.

Myocardial Infarction with Severe Shock:



Reduction of Mortality

"... in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

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Circulation

MARCH 1955
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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

The Cardiovascular Aspects of Marfan's Syndrome: A Heritable Disorder of Connective Tissue

By VICTOR A. MCKUSICK, M.D.

Clinically, Marfan's disease behaves as an abiotrophy of some connective tissue element. Cardiovascular manifestations result from defective aortic media, defective valve cusps, interatrial communication, and pectus excavatum. The defect of the aortic media manifests itself by dissecting aneurysm, diffuse aneurysm of the ascending aorta or a combination. Subacute bacterial endocarditis in a patient with Marfan's disease is described. Interatrial septal defect is less frequent than previously believed. Cardiac symptoms in severe pectus excavatum must be evaluated in light of possible Marfan's disease. Fifty families in which at least one *bona fide* instance of Marfan's disease has occurred were collected.

As part of a study of heritable disorders of connective tissue, the total genetic, clinical and pathological picture of Marfan's disease has been analyzed in 50 kinships in which at least one *bona fide* instance of this condition has occurred. The total number of definitely affected persons is approximately 105; this figure cannot be stated more dogmatically since, as might be expected, borderline cases were encountered in a number of the families.

A majority of the families for this study was discovered by examination of all available instances of congenital subluxation of the lenses; study of the individual patients and of their relatives revealed stigmata of Marfan's disease in approximately 70 per cent of these. Other specialities, particularly pediatrics, orthopedics and endocrinology, provided leads on cases. The Medical Examiner,* who is likely to see those cases of Marfan's syndrome which end in sudden death, has been another significant source of cases. Cases of dissecting aneurysm of the aorta from this source and from hospital pathology files have been studied from the point of view of inherited connective tissue abnormality of the Marfan type. Finally, the families of all cases ever diagnosed as arachnodactyly or Marfan's syndrome at the Johns Hopkins Hospital have been traced when possible and studied. The occurrence of multiple cases in many of these families, e.g., 15 in one, nine in a second, has swelled the total.

Other factors of this study,† including the

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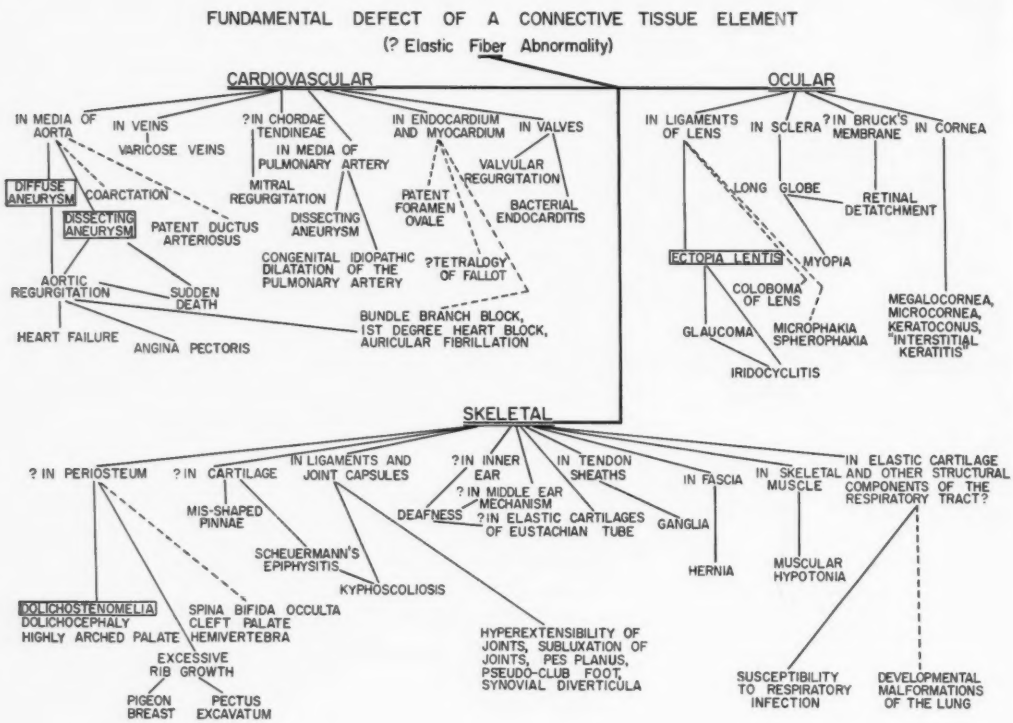
Presented in part at the meeting of the American Heart Association, Chicago, April 4, 1954. This investigation is part of a study supported by the Daland Fund of the American Physiological Society.

* The writer is indebted to Dr. Russell S. Fisher for permission to use the files of the Medical Examiner's Office of the City of Baltimore.

† The genetic data support the view that a single mutant gene is responsible for all aspects of this complex syndrome. One would suspect that there is, in some element of connective tissue, a basic biochemical defect, having widespread repercussions and resulting in the varied manifestations of this syndrome. The precise defect is yet to be identified. However, in a situation such as this it is possible to



MARFAN'S SYNDROME
A PEDIGREE OF CAUSES

genetic aspects, will be reported elsewhere. It is the purpose here to record the experience with abnormalities in the cardiovascular system. Such abnormalities, of at least mild degree, were detected in 46 individuals with possible abnormalities in 11 others.

It is convenient to discuss the cardiovascular aspects of Marfan's syndrome and to classify the cases according to the following outline:

I. Aorta:
   1. Dilatation of aortic ring.
   2. Dilatation of ascending aorta.
   3. Dissecting aneurysm.
   4. Combinations of 1, 2 and 3.
   5. Coarctation.
   6. Patent ductus arteriosus.

II. Pulmonary Artery:
   1. Dilatation (including some cases of so-called "congenital idiopathic dilatation").
   2. Dissecting aneurysm.
   3. Microscopic alterations of media.

---

construct a "pedigree of causes"[1] as is given in figure 1. The chart reviews the components of this syndrome. Special attention is directed to those manifestations indicated by interrupted lines: in the skeletal system, spina bifida occulta and hemivertebra; in the heart, interatrial septal defect and coarctation of the aorta; in the eye, coloboma of the lens and microphakia. In the present state of our knowledge these congenital anomalies of the more conventional type are difficult to explain on the basis of a unitary defect of connective tissue unless one assumes that the presence of this defect during embryogenesis produces an abnormal setting in which these particular anomalies occur with increased incidence. If this is true, these less frequent manifestations indicated by the interrupted lines may be considered secondary ones.

I I. Septal Defects:
1. Atrial.
2. Tetralogy of Fallot.
V. Valvular Abnormalities:
1. Stretching and sacculation of the aortic cusps.
2. Other gross and microscopic changes.
3. Subacute bacterial endocarditis.
V. Dysrhythmias and conduction defects.
VI. Pectus excavatum.

Aortic Lesions

A number of the early autopsies in cases of Marfan's syndrome, all infants and children, revealed patency of the interatrial septum. "Congenital heart disease" in general and this defect specifically came to be considered the cardiovascular hallmark of this disorder. As adult patients were recognized and studied, it became clear that a structural abnormality in the great vessels leads to manifestations which are both more frequent and clinically more significant. Although a very few references* to aortic abnormalities in association with arachnodactyly are buried in the earlier literature, the first definitive description of the two complications to which the aortic defect predisposes, diffuse dilation of the aorta[2] and dissecting aneurysm of the aorta,[3] appeared in 1943.

The early changes, which are more likely to be seen in cases dead of dissecting aneurysm, are indistinguishable from Erdheim's cystic medial necrosis. (Etiologically the latter may not be a homogeneous entity inasmuch as not all histologically typical examples can be correlated with clinical evidences of Marfan's syndrome.) The late changes, which occur characteristically in cases of dilatation of the ascending aorta, usually with profound aortic regurgitation, consist of 1—disruption of the elastic lamellae, 2—formation of conglomerate, disorganized masses of hyperplastic and hypertrophied smooth muscle fibers, and 3—formation of greatly dilated vascular channels penetrating the media from the adventitia. The net result is a thicker aortic wall than normal, but a weaker one.

The interpretation of the histologic findings and the deduction of pathogenesis from them are matters of disagreement. Some suggest that the large vascular pools, presumably a congenital anomaly, produce the other changes by local stagnant anoxia. More plausible, perhaps, is the pathogenetic chain of events proposed by Gore[4] and others. This view holds that "degeneration" of the elastic lamellae is of primary importance. Thereafter the smooth muscle fibers which normally have both their origin and their insertion on the elastic plates collapse together and, so it would seem, undergo compensatory hypertrophy and perhaps hyperplasia. May not the vascular changes observed be secondary to these smooth muscle changes?

The predominant involvement of the base of the aorta or most of the ascending aorta (in progressively lesser degree as one passes away from the heart, usually with rather sharp stopping of the alterations at the mouth of the innominate artery) is by no means inconsistent with this disease, it being a generalized disorder of some connective tissue element such

* One such instance is the case of a six year old child with aneurysm of the ascending aorta which ruptured into the pericardium, reported by Bronson and Sutherland in 1918.[55] "The unusual shape of his head and ears and the looseness of his joints attracted attention early in infancy." Inguinal hernia was repaired surgically at the age of two years and a left diaphragmatic hernia was discovered by x-ray examination. He was always undernourished but was sensitive and mentally advanced for his age with a quaint way of expressing himself and "a sense of humor of his own". The forehead was high and full, the palate highly arched. The ears were large without the normal folds of the pinnae. The joints were lax, the limbs flail-like and the elbows showed definite subluxation. There was lordosis and pigeon-breast with an increased prominence of the right side of the chest which showed better expansion. A pulsating mass was discernible to the right of the sternum. Although no diastolic murmur was mentioned, the left ventricle was hypertrophied at autopsy. There was also partial coaretation proximal to the left subclavian artery. It is impossible to imagine a better description of the condition under discussion here. The authors also presented a detailed review of reports previous to that time; many of these cases also are reasonably clear instances of Marfan syndrome.

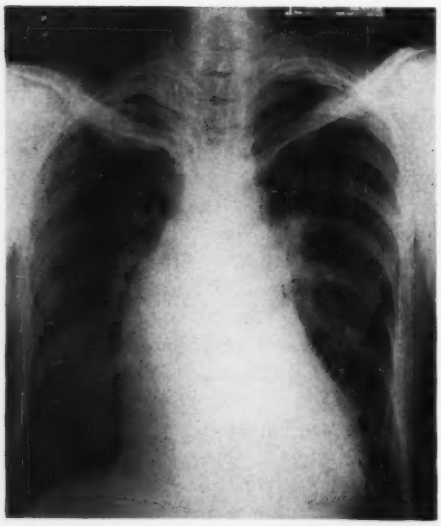


FIG. 2. Prominence of the main pulmonary artery and pulmonary conus and inconspicuous dilatation of the ascending aorta in a 49 year old man diagnosed as having rheumatic aortic and mitral lesions in spite of being very tall and having both spinal and thoracic deformities and ectopia lentis.

as the elastic fiber. Marfan's disease is an abiotrophy: the involved tissues wear out prematurely under the usual stresses and strains. The ascending aorta is subjected to pressures which are maximal for the arterial tree. As the pulse wave moves out in the vascular tree, the effective size of the elastic chamber into which the ventricle is ejecting is constantly increasing. The first sharp increase in the volume of this reservoir occurs at the innominate artery. There can be little doubt that the preinnominate ascending aorta is under maximal arterial stress and that this fact is, to a considerable extent, responsible for the localization of predominant involvement in both syphilis and Marfan's disease. The observations of Reynolds[76] that with physiological pulse pressures only the ascending aorta shows appreciable dilatation is probably pertinent in this connection.

Diffuse Aneurysm of the Ascending Aorta. When this particular abnormality occurs in Marfan's syndrome it is almost always limited to the ascending aorta, stopping abruptly just before the mouth of the innominate artery. (Clinically in case 3 of Thomas and coworkers[59] the descending aorta was also involved.) That the aortic ring and adjacent intrapericardial portion of the aorta are first affected is clear from the clinical course and has been demonstrated pathologically in cases dying before full-blown changes had developed.[5, 38] This feature is of great clinical significance since frequently these patients have profound aortic regurgitation with little or no demonstrable aortic dilatation. Syphilis, rheumatism, or bacterial endocarditis is often suspected first; when these appear unlikely from collateral evidence and when, as is so often possible in all sorts of disorders, a history of trauma is elicited, traumatic rupture of a normal aortic cusp is postulated.[6] Furthermore, a deceptive prominence of the pulmonic conus and main pulmonary artery may result from displacement of these structures by the dilated intrapericardial portion of the ascending aorta. This radiologic feature was very striking in case 2 of Baer and associates.[2] The pulmonary artery may, of course, be dilated as a result of intrinsic involvement of its media. Whatever the cause, the prominence of the pulmonary artery together with the Austin Flint murmur of aortic regurgitation leads frequently to the false diagnosis of rheumatic heart disease with combined aortic and mitral lesions. Such was the case in the patient, aged 49 years, whose chest x-ray is presented in figure 2, in spite of the fact that he was 6 feet 3½ inches tall, he had a spinal and thoracic deformity and had had ectopic lenses removed 10 and 13 years previously.

The aortic cusps, which probably participate in the same connective tissue defect, become enormously sacculated. Their defect may contribute to the aortic regurgitation. The stretching of the aortic cusps may proceed to the point that breaks with fenestration of the valve leaflets result.[11] At times the murmur of aortic regurgitation may be exceedingly loud and audible at a distance from the chest.[6, 64] It may have the musical "cooing" character commonly associated with rupture or eversion of an aortic cusp. Although, as mentioned above, traumatic rupture is frequently suspected, it is possible that such

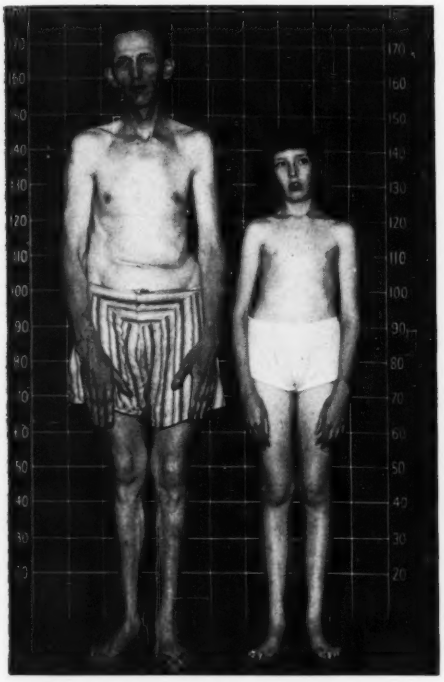


FIG. 3 A

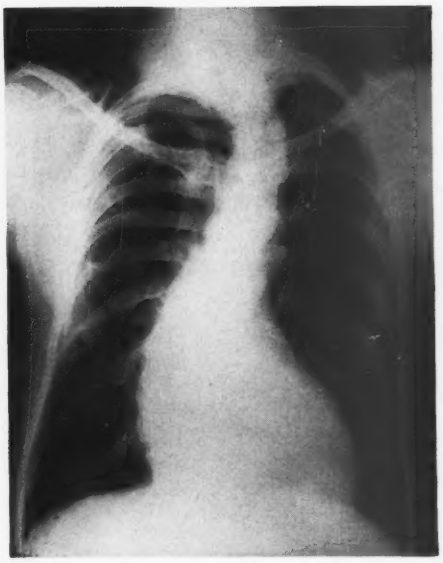


FIG. 3 B

FIG. 3. A. Both the man and his daughter have bilateral subluxation of the lenses, spinal curvature and dolichostenomelia (long, thin extremities). The man has had femoral and inguinal hernias repaired. The girl is only 9 years old. In 1950 the man had no cardiac murmurs. In 1953 he was found to have well-marked aortic regurgitation. B. The chest x-ray films of this man reveal no apparent dilatation of the ascending aorta. (The scoliosis obscures the picture.) Fluoroscopy likewise failed to establish dilatation of the aorta.

rupture of the defective aortic cusps may occur with or without physical strain in a patient with Marfan's syndrome.

By examining and following patients with ectopia lentis and their families, I have discovered three individuals who appear to be at the very inception of their aortic regurgitation. Figure 3 A and B presents such a case (the father). The aorta is not evidently dilated. In two of these very early cases the second aortic sound has a tambour quality reminiscent of that in syphilitic aortitis.

A number of years after aortic regurgitation is first observed these patients are likely to develop angina pectoris and left ventricular failure. The prognosis thereafter is identical with that of severe aortic regurgitation of syphilitic origin.[10] Most of the patients succumb within two years after the onset of significant symptoms. Granting the importance of other factors in the angina pectoris, one cannot help but wonder if one factor may not be the pronounced dragging of the large blood-laden aortic cusps on the coronary ostia. The coronary ostia become displaced to a higher position relative to the aortic commissures just as occurs in syphilitic aortitis.

Aortic dilatation with aortic regurgitation was the principal cardiovascular abnormality in at least 11 patients in this series. A boy was found to have the murmur of aortic regurgitation at the age of five years following a bout of pertussis and died at the age of 7¾ years. Another patient died at the age of 50 years, an aortic diastolic murmur having been first discovered 10 years before and bouts of left ventricular failure followed by right-sided failure having begun three years before. In a

reported case[52] dilatation of the ascending aorta with aortic regurgitation and marked left ventricular hypertrophy resulted in the death of a ten month old infant, and in another[75] death did not occur until the age of 55 years.

The patient presented in detail below is representative of the cases of aneurysmal aortic dilation in this series. An aortic diastolic murmur is known to have been present for at least nine years before death and seven years before the onset of left ventricular failure and angina pectoris. He lived 21 months after the onset of these symptoms. The correct diagnosis was not suspected until late because of inconspicuous dilatation of the aorta until the last year of life, failure to detect the ectopia lentis, and partial submersion of the characteristic habitus in the general pyknic build of the family from which the patient sprang. Earlier in the patient's course traumatic rupture of a normal aortic cusp was considered the probable diagnosis.

L. K. (J.H.H. 571745), a white man born in 1913, was first admitted to this hospital in May, 1951. On April 16, 1951, while riveting at an aircraft plant he noted the rather sudden onset of severe steady pain in his right chest radiating down the right arm. This disappeared in a few hours, and he was essentially asymptomatic thereafter, but was aware of profuse sweating particularly of the hands and feet.

Examination revealed that the blood pressure was 195/40/0. He was a slightly built man of average height. There was alternating external strabismus and the pupils were rather small but normally reactive. No other ocular abnormality was detected at that time. There were pronounced cardiac and peripheral signs of aortic regurgitation.

There was no history of rheumatic fever or syphilis and no laboratory or clinical evidence of syphilis or bacterial endocarditis. There was a story that in his work as a riveter the instrument which he held in front of his chest had, on several occasions, slipped, striking his chest forcefully. The possibility of traumatic rupture of an aortic cusp was considered most likely. In fact this was considered so likely by his physicians that with their assistance the patient succeeded in making a $4,000 settlement with his employer! The history of his having been previously turned down for insurance was not elicited.

The patient was virtually asymptomatic until September, 1951 when he began to have attacks heralded by very profuse sweating and consisting of pain under the lower sternum, severe palpitation and coughing. Rapid eating and excitement would precipitate the attacks. They occurred most often about midnight.

The patient's second admission was in May, 1952. At that time Dr. F. W. Dick first noted that the patient had iridodonesis bilaterally and that the edge of ectopic lenses could be seen with the ophthalmoscope. Since the age of 10 years the patient had worn glasses for myopia and bifocals since the age of 19 years. Examination revealed profuse sweating even in a cool room. The lid slits were wide and there was lid lag; these were interpreted as probably being related to the effort to accommodate. (The excessive sweating was probably that frequently seen with left ventricular failure.) The head was round and neck rather short. There was kyphosis without scoliosis. Muscular development was on the whole rather poor. The shoulders were rounded and scapulae moderately winged. His height was 5 feet 7 inches, fingertip-to-fingertip span 5 feet 11 inches. Pubic symphysis to heel dimension was 34 inches (over half his total height). There was syndactylism of the second and third toes bilaterally. At this time there was a diastolic thrill at the right border of the sternum and mediastinal dullness was increased to the right.

It was now very apparent that the patient had Marfan's syndrome. Superannuated dissecting aneurysm of the aorta was considered likely.

The remainder of the patient's life was characterized by severe attacks of sweating, anginal pain, and orthopnea. At no time were there signs of right-sided failure. Comparison of early and late films are presented in figures 4A, B, C, D The patient died Jan. 23, 1953.

At autopsy (#24360) his height was determined to be 5 feet 6 inches. (There is a discrepancy among the various reported measurements.) The kyphosis was again described. The significant findings were limited to the heart which weighed 980 Gm. (fig. 4C). The increased weight was almost entirely the result of very marked left ventricular hypertrophy. The ascending aorta was the site of pronounced fusiform dilatation. The aortic valve ring was dilated to about four times the normal circumference. The sinuses of Valsalva were greatly dilated and the aortic valve cusps themselves were relatively enormous baggy structures. The aortic dilatation stopped at the mouth of the innominate artery. Beyond the mouth of the left subclavian the aorta narrowed sharply in a typical, although only partial (about 40 per cent), stenosis of the isthmus.

Microscopic sections of the aorta (see figure 4D) revealed replacement of most of the media by scar tissue. There were some areas of cystic medial degeneration. Elastic tissue stains revealed marked

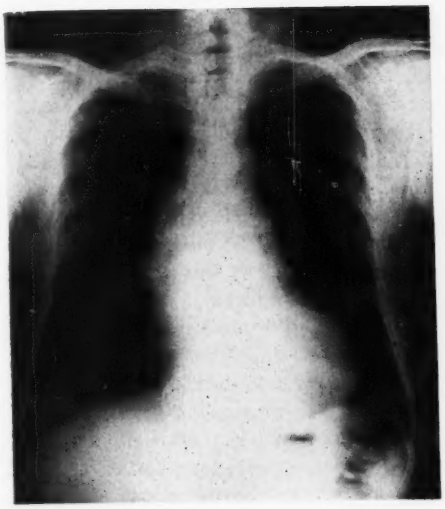


FIG. 4 A

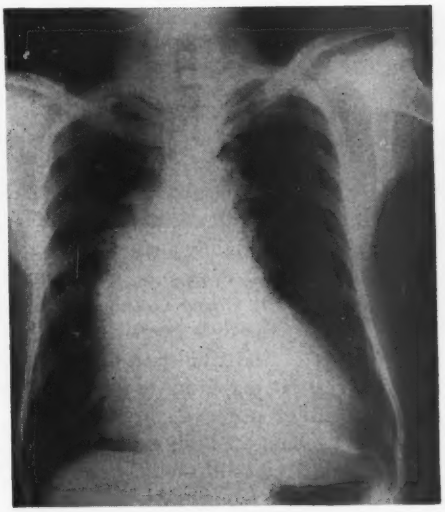


FIG. 4 B

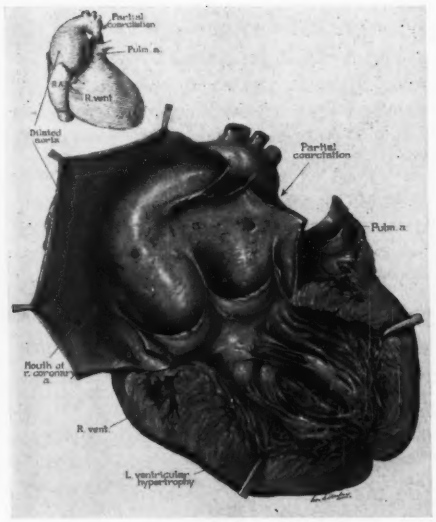


FIG. 4 C

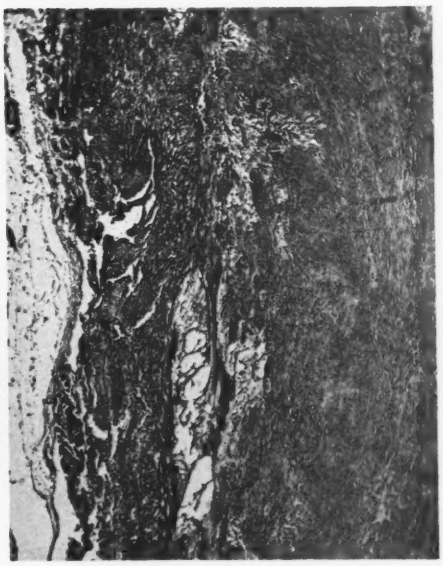


FIG. 4 D

FIG. 4. A. Dilatation of the ascending aorta is present but is not impressive. (Film taken 18 months before death in patient L. K.) B. A film four months before death in patient L. K. C. A sketch of the heart and great vessels as visualized at autopsy in patient L. K. Mild coaretation was present. Dilatation limited to the ascending aorta and tremendous sacculation of the aortic cusps are conspicuous features. Note the high relative position of the coronary ostia. D. Histologic section from the ascending aorta in the case of the patient L. K. See text.

disruption, fragmentation and sparcity of elastic fibers.

After the death of the patient, an investigation revealed, in the records of an insurance company, information that the patient was turned down for insurance in 1944 because of aortic regurgitation. Therefore an aortic diastolic murmur had been present for at least nine years before death and for

several years before symptoms of significance. It should also be noted that he had had varicose veins which required surgical treatment.

Comments. A point of great diagnostic interest and importance is illustrated by the x-ray films shown in figure 4, namely the fact that the aorta was not conspicuously dilated at the time the patient was first seen, in spite of the presence of striking aortic regurgitation. A possible useful point may be in the finding at fluoroscopy at the time of the first admission that "the lower right border of the heart in the region of the right atrium showed a marked increase in amplitude of pulsation. The pulmonary artery segment on the left side of the heart also pulsated vigorously, although the vascular markings of the lung were if anything decreased." As pointed out above, in some of these cases the outflow tract of the right ventricle and base of the pulmonary artery are evidently displaced forward and to the left (by the dilatation of the base of the aorta), simulating enlargement of these structures.[7] On the other side the intrapericardial portion of the aorta may be responsible for displacement and active pulsations in the right atrium.

A feature of equal diagnostic significance and of considerable genetic interest is the relative submersion of the full-blown skeletal manifestations when the Marfan mutation occurred in this pyknic stock. When first seen the patient did not impress anyone as being beyond the normal range as to habitus. Discovery of ectopic lenses resulted in the observer being more impressed with the habitus. Comparison with his brothers and sisters would likewise have impressed the physician with the patient's abnormality. Other members of the family were about 5 feet 3 inches tall and were very heavily muscled with short powerful extremities and stubby fingers. The moral to the diagnostician is obvious. Although extensive studies of the families were not undertaken, several cases in the literature probably illustrate this same phenomenon.[8]

This case bears many resemblances to case 3 of Tung and Liebow.[9] The type of aortic involvement which they illustrate is almost identical to that in figure 4C. Their patien , who died of aortic insufficiency at age 42, ha l had two herniorrhaphies and had varico e veins. Although the authors state that "n o suggestion of arachnodactyly nor of any othe r external sign of Marfan's syndrome (was) re - corded by any of several senior physicians wh o were concerned with the care of this man," it must be noted that he died in 1932 which wa s before a single case of this syndrome had bee n reported in the internal medical literature o f this country and over 10 years before the asso - ciation of aortic dilatation and arachnodactyl y was first clearly described.[2]

Dissecting Aneurysm. The same lesion whic h may result in diffuse dilatation may be th e basis for dissecting aneurysm of the aorta . In fact the two complications occasionall y coexist (see figure 3 in ref. 42 and figure 2 in ref. 54). This is, then, another mechanism for an association of the murmur of aortic regurgitation with dissecting aneurysm.[46] That the lesions are not necessarily limited to the ascending aorta is indicated by cases of arachnodactyly and dissecting aneurysm in which dissection and cystic changes were observed in the abdominal aorta.[11, 12] In case K. B. reported below, two dissections were present in the aorta, one proximal and one distal to a partial coarctation. In a patient described by Weve[58] in 1932, laparotomy revealed aneurysm of the aorta extending from the diaphragm into the pelvis. Sudden death on the basis of dissecting aneurysm with rupture into the pericardial sac or pleural cavity was demonstrated to have occurred in several patients of this series and from the history is suspected to have occurred in several others.

To my knowledge the oldest patient succumbing to this complication of Marfan's syndrome was 52 years old;[12] a 48 year old patient dying of dissecting aneurysm on this basis was discovered in this series.

At least one patient in this series survive d the acute dissection for about two year s, demonstrating aortic regurgitation which fro m autopsy evidence appeared to have been du e principally to distortion of the aortic ring b y

the intramural hematoma. In one case[13] described as "chronic dissecting aneurysm of the aorta resembling chronic rheumatic heart disease" historical and physical features typical of Marfan's disease are enumerated although the existence of a generalized connective tissue abnormality was apparently not appreciated by the authors. In still another case reported as "chronic dissecting aneurysm simulating syphilitic cardiovascular disease,"[14] Marfan's syndrome mimicked the "Great Mimic." The occurrence of aortic regurgitation with dissecting aneurysm is well recognized in this country since Resnick and Keefer's description in 1925.[45] Hamman's explanation (distortion of the aortic ring by the intramural hematoma) is the usually accepted one.[46]

A combination of terminal dissection of the aorta with previous dilatation of the ascending aorta occurred in several of the patients in this series including the two Medical Examiner's cases who are described briefly below:

1. R. L. L., a 37 year old unmarried white man, dropped dead on March 19, 1953, while being interviewed for employment. Necropsy revealed dilatation of the ascending aorta and dissection of the aorta with rupture into the pericardial sac. From the application form he had just filled out for employment and from conversations with his parents in a distant state, the following facts were pieced together. He was 74½ inches tall and weighed 220 pounds. He had always been stout. "A cartilage" projected on one side of the front of his chest. He had flat feet and knock-knees for which he was turned down for the Army but subsequently was taken into the Air Corps where he served four years and attained master sergeant rating. His knees gave him much trouble and required operation while he was in the service. For several years before his death his family noted a collapsing type of active pulsation in the neck. He was dyspneic on climbing stairs but this was attributed to obesity. He lacked his usual energy. After his death digitalis was found on his person and it was found that unknown to his parents with whom he lived he had been under medical care for some time. This appears to have been a sporadic case inasmuch as a sister, the parents, grandparents, aunts, and uncles, appear to be unaffected by anything resembling Marfan's disease.

2. W. W., a 24 year old white boy, died suddenly on July 8, 1944, following a high dive. Necropsy revealed dilatation of the ascending aorta and dissecting aneurysm with rupture into the pericardial sac. This patient was 73½ inches tall and is described by his father as having been "well built." He was an active wrestler, ice skater, swimmer. He was turned down by the Selective Service examiners about 18 months before his death because of aortic regurgitation. He was advised not to dive. No eye abnormality was known and he had had no trouble with hernia or flat feet. He was employed in war industry in Baltimore at the time of his death.

The parents and two siblings are said to be well although there has been no opportunity to examine these individuals who live in another part of the country. A paternal uncle, 75 inches tall, died of "leakage of the heart" at the age of 60 years. He had, however, had rheumatism in younger years.

Other Aortic Abnormalities. Coarctation of mild degree, and of the adult type, was present in patient L. K. above and patient K. B. below. It has been previously described in patients with Marfan's syndrome.[11, 15] Two patients had patent ductus arteriosus and this, too, has been seen before.[16] As mentioned in the footnote on page 2, these may be considered secondary manifestations of this condition. It is doubtful whether there has ever been a case of Marfan's syndrome with coarctation severe enough to be of clinical significance. (One patient in our group has hypertension and a small left radial pulse but no discrepancy in arm and leg pressures.) However, it is probably wise to be on the lookout for stigmata of Marfan's syndrome whenever either coarctation or patent ductus is encountered.

Whitfield, Arnott and Stafford[49] described a case of simple hypoplasia of the aorta with Marfan's syndrome. They suggested that the increased resistance produced by the reduced aortic diameter might have been at least partially responsible for the cardiac hypertrophy in this case. Since hypoplasia of the aorta is a questionable explanation for symptoms or signs under any circumstances, the interpretation of these authors is doubtful. In at least one reported case,[51] bacterial endaortitis was thought to be present, producing the clinical picture of subacute bacterial endocarditis. The site of infection was probably the first part of the descending aorta.

Pulmonary Artery Lesions

Baer, Taussig and Oppenheimer[2] described the same lesions in the pulmonary artery as occurred in the aorta of their two patients. However, these lesions were not sufficiently pronounced to have been of functional significance. Tung and Liebow[9] have described the case of an infant in which the pulmonary arterial abnormality was of real clinical significance, and also that of an adult with a clinical picture which would justify the label of "idiopathic congenital dilatation" of the pulmonary artery. We have seen cases of both types and presented below is an example of the first. Anderson and Pratt-Thomas[17] have recently reported another case in which involvement of the pulmonary artery dominated the clinical picture. In this patient rupture of the pulmonary artery into the pericardial sac occurred. In retrospect, surveys of the literature reveal cases which, from ancillary information, were almost certainly cases of aneurysm of the pulmonary artery on this basis.[5,6]

"Idiopathic congenital dilatation" of the pulmonary artery[18] is almost certainly not a homogeneous group. In some of the cases there is hypoplasia of the aorta. It has generally been considered a benign condition. If there is any reason to suspect that this is merely one component of Marfan's syndrome, the prognosis is, of course, quite different. Dissecting aneurysm occasionally occurs in the pulmonary artery on the basis of the medial abnormality of Marfan's disease.

In the infant described below, pulmonary artery involvement was of primary significance.

B. J. P. (H.L.H. A93754) was born Nov. 9, 1951. She weighed 6 pounds, 11 ounces, and was thought to be healthy. The mother had had no pregnancies in the 19 years between this one and that which occurred in 1933. The mother first learned of the child's heart murmur when the child was four months old. The child was never able to sit up or roll over by itself. When first seen at the age of six months, the following findings were recorded: The left side of the face was smaller than the right. Respirations were rapid (about 50 per minute). There was a pigeon breast deformity of the thorax. The pulse was regular at a rate of 150 per minute. Femoral pulses were full. The heart was enlarged beyond the left midclavicular line. A systolic thrill was palpable over the entire precordium but was maximum in the left midprecordium. A harsh systolic murmur had the same location. The liver edge was 1.5 cm below the right costal margin. There was no clubbing or cyanosis.

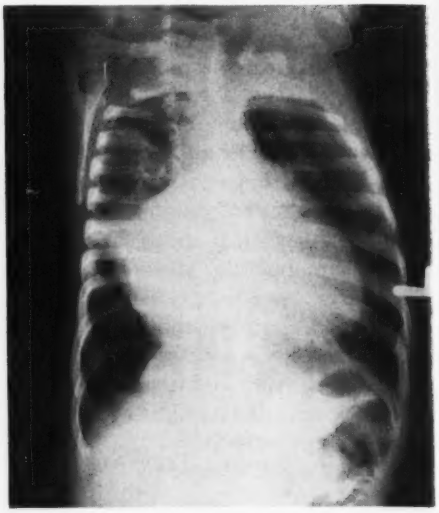


Fig. 5. X-ray film of the chest in infant B. J. P. The pulmonary anomaly is evident as well as the pronounced cardiomegaly.

Fluoroscopy (see figure 5) revealed great cardiac enlargement to both left and right with globular shape. The right ventricle was definitely enlarged in the oblique views. The right lower lung field had a distinctly abnormal appearance. It lacked the usual lung markings and was unusually radiolucent. There was a question of atelectatic lung (? right middle lobe) at the right heart border. By electrocardiogram the P waves were broad and notched. The P-R interval was 0.16 second which is long considering the patient's age and heart rate of 150 per minute. Very large R waves in the leads from the left of the precordium suggested left ventricular hypertrophy. The hematocrit was 29.5 per cent with hypochromic, microcytic cell indices.

Late in May, 1952 the patient developed physical and x-ray signs of consolidation in the right upper lobe and became febrile. These signs were altered little by the administration of several different antibacterial agents. The heart was extremely overactive and shook the whole bed. Occasionally the murmur assumed a to-and-fro quality, especially at the lower left sternal border. The liver enlarged in size. Subsequently signs of consolidation of the entire right lung appeared. On July 31, 1952 it was noted that both lenses were misplaced mediad and

t at dilatation of the pupil with phenylephrine was o ly partially successful. Ophthalmologic consultants o served that the patient was extremely myopic v ith small lenses. In the last weeks of life there was a episode of hematuria related, perhaps, to sulfa- azine therapy. Death occurred on July 10, 1952 v hen the patient was only 8 months old.

Autopsy (#23761) revealed that the right lung v as partially atelectatic. The left lung was normal. The pulmonary artery was larger in circumference t an the aorta. The foramen ovale was imperfectly c osed. All chambers of the heart showed hyper- t ophy of their walls and dilatation. The hyper- t ophy of the right atrium was particularly marked Microscopically there were no lesions of the myo- cardium. However, the wall of the pulmonary artery and to a lesser extent that of the aorta showed typical changes of Marfan's syndrome. The media contained vacuoles filled with metachromatically staining material and there was derangement and relative sparcity of elastic fibers. The wall of the pulmonary artery was thicker than that of the aorta. At the time of the gross examinations the bronchial tree was injected with radio-opaque material and radio- grams were made. To the surprise of the prosector no abnormality was identified.

Comments. Obviously the most informative feature of this case is the advanced change in the pulmonary artery which undoubtedly resulted in pulmonary regurgitation and was a leading factor in the infant's death at the age of only eight months. Ectopia lentium, myopia, microphakia, arachnodactyly, retardation of ability to sit or roll over complete the picture of Marfan's syndrome.

This kinship illustrates one of the difficulties of genetic research in man. The illegitimacy of this infant and the presence of a legitimate wife made the utmost tact and resourcefulness necessary for collecting even these few data. The father of the infant is about 74 inches tall, has long hands and feet, and wears spectacles. Examination was not possible and no further pedigree information was obtained.

Interatrial Septal Defect

This lesion, the incidence of which in Marfan's syndrome was exaggerated by earlier reports, is of real functional significance in occasional patients. The 12 year old girl described below is such a case. Almost all the cases[2, 12, 19, 20, 21] are ones of patency of the foramen secundum (foramen ovale); the foramen primum type of patency has been described with certainty in only one autopsied case.[22] Abnormality of the interatrial septum is possibly, like coarctation and patent ductus arteriosus, a secondary manifestation of the connective tissue defect.

One would expect that the combination of interatrial septal defect and inherent weakness of the pulmonary arterial wall might result in even more dilatation of the pulmonary artery than is usually seen with either lesion alone. This has not been demonstrated with certainty, however.

M. E. C. (J.H.H. A98174), born in 1940, was first referred to Dr. Helen B. Taussig in Nov., 1952, for investigation of her congenital heart defect and paroxysmal tachycardia. The father is 76 inches tall and very asthenic and has a spinal curvature and ectopia lentis but no evidence of cardiovascular abnormality.

In this case a heart murmur had been described before the age of two years. Except that she never gained weight well and could not keep up with the other children at play, the patient was relatively well until April, 1952, when she had a first attack of paroxysmal tachycardia lasting several hours. Two more attacks occurred, one in May and a second in Sept. 1952.

The patient was a tall, slender white girl of better than average intellect. She was 64 inches tall and weighed 79 pounds. She wore glasses for ectopia lentium, which had been discovered at the age of five years. The palate was high. The chest was long with convex scoliosis of the thoracic spine toward the right. The heart was not enlarged. However, a loud systolic murmur accompanied by a thrill was heard in the second and third intercostal spaces to the left of the sternum. The patient stood with rather marked pronation of the feet at the heels and moderate abduction. There was minimal genu valgum.

On fluoroscopy (see figure 6) the right atrium was seen to be enlarged and the main pulmonary artery was prominent and active. There was moderate hilar dance. The left atrium and the ventricles appeared to be normal in size. During the recording of the electrocardiogram short paroxysms of atrial tachycardia occurred. There was a higher degree of right axis deviation than would have been anticipated even at this age. Leads II and III showed changes in the ST-T complex interpreted as "right ventricular strain pattern." The QRS complexes

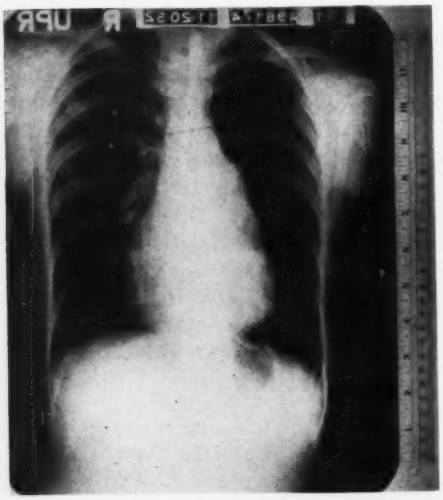


FIG. 6. Chest x-ray film in M. E. C., an instance of interatrial septal defect with Marfan's disease.

were notched in most leads. X-ray films revealed no structural abnormality of the vertebrae.

Surgical repair of the interatrial defect is probably worthwhile in this patient in spite of the presence of a generalized disorder of connective tissue which may express itself elsewhere in the cardiovascular system.

IS TETRALOGY OF FALLOT AN OCCASIONAL MANIFESTATION OF MARFAN'S SYNDROME?

We have encountered two patients with tetralogy of Fallot who have suggestive stigmata of Marfan's disease. In these cases the diagnosis of tetralogy is not in question although that of Marfan's disease is. Careless statements in the review literature notwithstanding, interventricular septal defect has never been established in a case of arachnodactyly. (In Cockayne's case[23] ventricular septal defect was suggested on clinical grounds alone and even this evidence was scanty. There is a report[47] of a possible tetralogy of Fallot with arachnodactyly.) The cases in this series had the Blalock-Taussig operation for tetralogy of Fallot and both had arachnodactyly but no ectopia lentis. In neither case were there stigmata of Marfan's syndrome in the other members of the family. One of the cases (J.H.H. 525256) had malformed pinnae and spinal curvature from hemivertebra (fig. 7). The other patient (J.H.H. 482041) had cleft palate, pes planus, and talipes equinovarus.

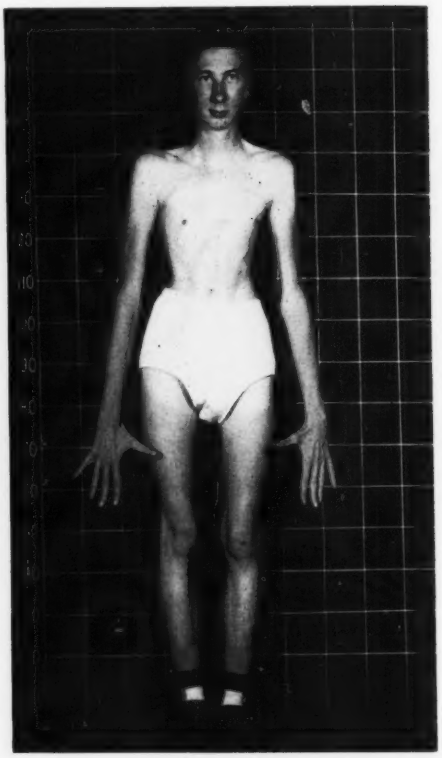


FIG. 7 A

FIG. 7. A. A case of tetralogy of Fallot and possibly Marfan's syndrome. Note facial asymmetry, deformity of the pinnae and long fingers. B. Hemivertebra in the same case.

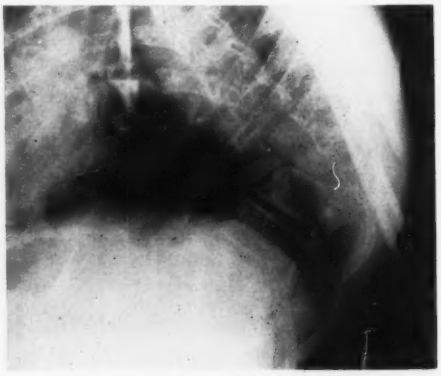


FIG. 7 B

Valvular Changes and Bacterial Endocarditis

Unexplained or poorly explained precordial systolic murmurs occur commonly in these patients. Redundancy of the chordae tendineae may be the basis of the murmur in some cases. The state of the chordae tendineae is often difficult to evaluate at necropsy because of the other gross abnormalities, especially ventricular enlargement. The thoracic deformity may be responsible for the systolic murmur in some instances.

Marginal thickening and nodular excrescences of the valve cusps, particularly of the mitral valve, occurred in a rather high proportion of autopsied cases.[20, 38, 52] Tung and Liebow[9] have described cystic changes in the mitral valve cusps with deposition of the same metachromatic coagulum as occurred in the aorta in the same case. On these valve changes bacterial endocarditis may apparently be engrafted. Bacterial endocarditis under these circumstances was reported at least twice previously[24, 57] and occurred in the following pregnant patient with Marfan's syndrome:

M. E. R. (J.H.H. 176836), a colored female born in 1929, is a member of a family which has been known to this hospital for about 25 years and in which at least 10 cases of Marfan's syndrome (including this patient) have occurred. (The patient is individual III-11 in the pedigree presented in figure 8A.) The father of the patient, a well-documented instance of this syndrome, died of dissecting aneurysm of the aorta at the age of 43 years. Of four siblings of the patient with this disease three have signs consistent with interatrial septal defect.

The patient demonstrates bilateral ectopia lentis, severe myopia, pronounced dolichostenomelia, very poor muscular development, severe kyphoscoliosis, pes planus, and by x-ray films pulmonary emphysema with bleb formation. The patient is shown in figure 8B. She recalled nothing suggestive of acute rheumatic fever. Most of her life she had been subject to exertional dyspnea.

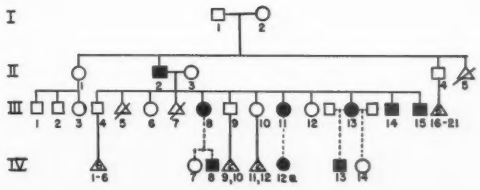


Fig. 8 A

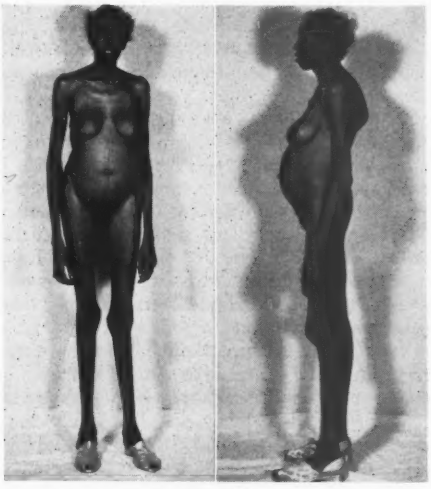


Fig. 8 B

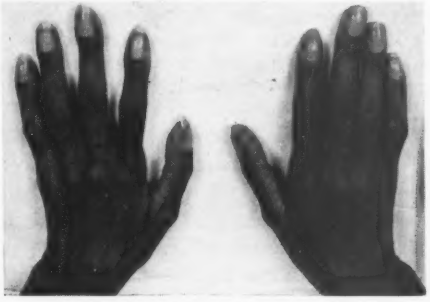


Fig. 8 C

Fig. 8 D

Fig. 8. A. Pedigree of the family of patient M. E. R. (III-11). Individual II-2 appears to have been the original mutant. B. Patient M. E. R. C. The combination of arachnodactyly and clubbing of the fingers relates to the Marfan's disease and subacute bacterial endocarditis from which the patient M. E. R. suffered. D. The mitral valve showing bacterial vegetation.

The patient became pregnant in early November 1953. After about four months there was increase in her life-long exertional dyspnea and the appearance of ankle edema and orthopnea which required two pillows. In early April 1954, there was onset of evening fever, nightsweats, and aching joints, especially knees and ankles. Tender red spots appeared on the palms and soles.

Physical examination revealed as new findings petechiae, embolic nodes of the palms, splinter hemorrhages of the nail beds, and clubbed fingers. A loud harsh systolic murmur was audible over the entire precordium and the second pulmonic sound was accentuated.

Six blood cultures demonstrated a streptococcus viridans which was late in growing out and atypical in morphology due probably to streptomycin and penicillin which had been administered before admission to the Osler Medical Clinic. The patient's white blood cell count was 10 to 12,000 and hematocrit 26 per cent. Treatment with penicillin in large doses was instituted with seemingly successful results. Figure 8C reveals the unusual combination of arachnodactyly and digital clubbing.

On the patient's twentieth day in the hospital premature labor began and an infant weighing 1700 Gm. was born. The infant, which demonstrated pronounced dolichostenomelia, lived only a very few minutes. Autopsy in the case of the infant revealed no cardiovascular lesion and the cause of death is not completely clear.

The patient died of uncontrollable heart failure about two weeks after delivery. Figure 8D shows the mitral valve with its vegetations in this case. No evidence of rheumatism was discovered. The media of the aorta was histologically normal.

Comment. It is, of course, impossible to be certain that the patient did not have a rheumatic lesion of the mitral valve on which her bacterial endocarditis was engrafted. It is by no means necessary that such is the case; Marfan's syndrome is adequate basis for all the developments in this case.

Dysrhythmias and Conduction Defects

Abnormalities of these types were encountered in a number of the patients of this series. Most of these abnormalities were probably functional consequences of the stresses and strains imposed by the other dysfunctions, principally aortic regurgitation and interatrial septal defect. Atrial fibrillation is known to have occurred at least six times. Paroxysmal atrial tachycardia occurred in the case of interatrial septal defect described above. Delayed atrioventricular conduction occurred in several cases with aortic regurgitation as did also left bundle branch block. Others have reported bundle branch block[60, 61, 62] and partial atrioventricular block.[2, 60, 61]

One patient, now 18 years old, with unequivocal ocular and skeletal signs of Marfan's disease has right bundle branch block as the only cardiovascular abnormality demonstrable by extensive studies which included cardiac catheterization. A brother of this patient, who probably suffers from a *forme fruste*, demonstrates inverted P waves bespeaking an ectopic pacemaker. The father, who had aortic regurgitation and died suddenly at the age of 28 years, had either ectopic pacemaker or prolongation of the P-R interval with superimposition of P waves on T waves.

Pulmonocardiac Failure

Very pronounced kyphoscoliosis occurs in some of these patients, due usually to laxity and redundancy of the spinal ligaments but occasionally to hemivertebra (figure 7). It is remarkable that in no case has this thoracic deformity been clearly the cause of even a portion of the cardiovascular dysfunction observed. Particularly is this surprising in light of the fact that these patients seem to be prone to repeated pulmonary infection which is certainly an important factor in the cor pulmonale of kyphoscoliosis.

The Cardiac Effects of Pectus Excavatum

Very severe pectus excavatum has been observed in some cases of Marfan's syndrome. The two types of chest deformity which may occur, pigeon breast and pectus excavatum, are apparently the result of excessive longitudinal growth of the ribs resulting in either projection or depression of the sternum.

Much has been written about cardiac disability resulting from pectus excavatum.[63, 65, 66, 67] Furthermore, since originally proposed by Flesch[69] in 1873, excessive longitudinal growth of the ribs has been thought to

be the mechanism in many of the cases. The hereditary nature of the disorder has frequently been evident.[68, 70, 71, 72] Many of the patients with this chest deformity are described as unusually tall and thin with spinal curvature. In spite of these facts, it has not been appreciated that many of the patients with pectus excavatum are victims of a generalized disease which may have affected the cardiovascular system directly. In two surgical reports,[25, 27] there are three cases of pectus excavatum in which follow-up[26, 73] has established the diagnosis of Marfan's disease. At least two other possible cases of Marfan's disease reported in the surgical literature as being instances of pectus excavatum with secondary cardiac effects are 1—the six-year-old patient described by Lester[74] as having "systolic and diastolic murmurs and cardiac incompetence" and 2—the patient of Ravitch,[28] a 23-year-old, 74-inch-tall man who had congestive heart failure and atrial fibrillation and who was specifically described by his physician as thin, gangly, loose-jointed and round-shouldered.

Without question simple pectus excavatum of severe grade can be accompanied by dyspnea, pain, and atrial dysrhythmias. It also can produce loud systolic murmurs. Whether it alone produces congestive heart failure in young individuals, requires careful re-examination of the patient and the medical status of other members of his family.

Although physical signs are difficult to interpret in the presence of pronounced thoracic deformity, a basilar diastolic murmur must be considered, in the light of our present knowledge, an indication of aortic involvement and a contraindication to surgery for sternal malformation. The Graham-Steell type of pulmonary diastolic murmur sometimes heard in kyphoscoliotic heart disease need not be a source of confusion.

In general, surgical repair of the pectus excavatum has been as successful in these cases as in those without the rest of Marfan's syndrome. Healing is not impaired, according to the observation of surgeons who repair the hernias, close cleft palates or remove ectopic lenses in these cases. (See ref. 52 for an exception.) However, it is recommended that correction of pectus excavatum in Marfan's syndrome be postponed until after puberty when rib growth has ceased.

The following case demonstrates two complications of Marfan's disease. Severe pectus excavatum was present and in the period following operation for repair of this deformity, fatal dissecting aneurysm of the aorta occurred. An aortic diastolic murmur had been present before operation. Like case W. W. above, dilatation of the ascending aorta almost certainly preceded the development of the dissecting aneurysms.

K. B.,* a 24 year old white man, was admitted to the Medical College of Virginia Hospital after a year of increasing dyspnea. Twenty-four days before admission he had suddenly become markedly dyspneic and had severe palpitation and substernal pain. About two weeks before admission he had a second episode of pain and palpitation. Following the first attack his dyspnea progressed more rapidly than before and he also became orthopneic.

Physical examination revealed a slender, underdeveloped, undernourished man who was dyspneic even at rest. There was pronounced pectus excavatum (figure 9). The heart was markedly displaced to the left with the point of maximum impulse in the midaxillary line and the seventh and eighth intercostal spaces. The left anterior chest wall heaved with each heart beat. There was a loud continuous machinery-like murmur over the base of the heart with a systolic thrill. Blood pressure was 90/40 in the right arm and 110/32 in the left.

On Nov. 5, 1949 surgical repair of the pectus excavatum was performed.[27] The patient withstood the operation well and remained in a satisfactory condition until 48 hours later when he suddenly went into circulatory collapse and died in less than two hours after developing pronounced distension of the cervical veins.

At autopsy the body measured 72 inches in length. The arms and legs were very slender and long with poor muscular development. The left leg was shorter than the right and showed partial club foot. Bilaterally the first and second toes were unusually long but the fourth toes shorter than normal. There were flexion deformities of the fingers, deformed teeth with malocclusion, bifid uvula, and lumbar kyphosis.

The heart weighed 550 Gm. The increase in

* This patient is included through the courtesy of Drs. W. B. Porter and I. A. Bigger.

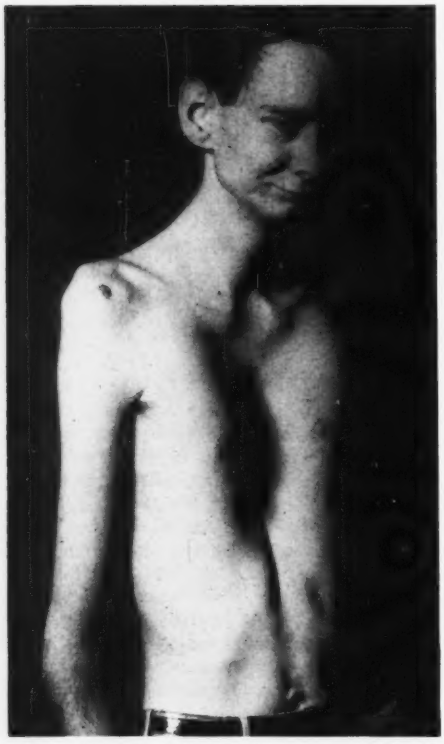


FIG. 9. Demonstration of the pronounced pectus excavatum in patient K. B.

weight and size was the result of left ventricular hypertrophy and dilatation. The pericardial sac contained 880 cc. of blood. The ascending aorta and first portion of the arch were markedly dilated and in addition there was a dissecting aneurysm of the wall extending from an intimal tear about 3 cm. above the aortic ring to the point where there was slight coarctation of the aorta between the left subclavian and left common carotid ostia. Just distal to the left subclavian a second dissection began and extended throughout the rest of the aorta to involve the first portion of both iliac arteries. A small rent on the anterolateral surface of the ascending aorta represented the spot where perforation into the pericardial sac had occurred.

Histologically both dissections were endothelialized and showed some atheroma formation. In addition the media showed pronounced changes of the types described in other cases of aortic abnormality in this series, particularly L. K. above.

OTHER CARDIOVASCULAR ABNORMALITIES

Except for one report[47] of dilatation of the left external carotid artery (not studied anatomically), no evidence of abnormality in peripheral vessels has been discovered. Dissection may extend out from the aorta an appreciable distance into the peripheral arteries but these have been histologically normal.[19] No pericardial peculiarity such as diverticulum or cyst, has been reported.

COEXISTENT CARDIOVASCULAR LESIONS

Rheumatic Fever. It was suggested by Futcher and Southworth[29] that patients with Marfan's disease may have more than average susceptibility to rheumatic fever. In addition to their case, at least three patients in this series had illnesses consistent with the diagnosis of rheumatic fever. Whether this represents an abnormally high incidence is difficult to state. Certainly the incidence is not striking. Furthermore, in no instance has an unmistakable rheumatic lesion such as mitral stenosis been found clinically or *post mortem* in a patient with arachnodactyly.

Syphilis. A reported case[30] and at least four of my cases have had positive serological tests for syphilis. Two of these patients had severe aortic regurgitation with death after brief illnesses. Autopsy was unfortunately not performed. The combination of syphilis and Marfan's syndrome might be expected to have dire effects on the aorta. Congenital syphilis was present in a recently reported patient with aortic dilatation.[58]

Hypertension. Two of my patients appear to have essential hypertension. Although the aorta at their present ages of 27 and 25 years shows no abnormality clinically, the hypertension may place them in additional jeopardy from dissecting aneurysm and the other aortic complication of their connective tissue disorder. A patient with Marfan's disease and malignant hypertension has been described to me by Dr. Milton Landowne.

Pregnancy. There is suggestive evidence that dissecting aneurysm of the aorta occurs with increased incidence in pregnancy. (In one review[31] of 49 cases of fatal dissecting aneurysm in females under the age of 40 years, about one-half were pregnant women.) The mechanism is unknown. A general loosening of connective tissues, apparently on a hormonal

lasis, is striking in lower animals including monkeys. Some orthopedists have the impression that a similar loosening of articular structures occurs in human pregnancy. In spite of these theoretical considerations pregnancy has not been observed to have any ill effects on the patients we have followed. But the 23 year old patient with Marfan's disease, reported by Lindeboom and Bouwer, was pregnant when she succumbed to dissecting aneurysm.[50]

An Unusually Severely Affected Family

By way of summary, herewith the story of a family which was unusually heavily affected by the cardiovascular complications of Marfan's syndrome. Figure 10 presents the pedigree of this family, affected probably through at least four generations. Individual I-1 died suddenly in 1897 at the age of 47 years, presumably of apoplexy. This may have been dissecting aneurysm. The son of this man (II-5) died at the age of 27 years after a very brief illness of undiagnosed nature. He was six feet tall, was always very thin and had been sent to Texas at one point for suspected tuberculosis. He became ill at noon one day and was dead at 5 a.m. the following day. He was said to have had no pain but developed hematuria in the late afternoon of the day he became ill.

Most of the remainder of the story of this family is told in the words of individual II-6, an intelligent observer and cooperative informant. Her husband (III-5) died in 1945 at the age of 32 years. "His heart condition was diagnosed as endocarditis by a heart specialist. He was apparently in good health up to two months prior to his death. He was 6 feet 2½ inches tall and in the last two years of his life he weighed more than ever before—175 pounds—and appeared to be in excellent health, except for his failing eyesight. He was working exceptionally hard due to the wartime manpower shortage. He was appointed to a job which necessitated a great deal of coast-to-coast flying at high altitudes. It was on one of these trips that he was taken ill. He returned home, was put to bed and given medicine to which he responded beautifully. He insisted on going on another trip and lived one month after his return. He was hospitalized but his case was pronounced hopeless. He had a hernia operation two years before his death. A routine check-up before the anesthesia showed no heart condition then.

The daughter of this man (IV-7) "was born May 17, 1937. She was always frail. She and her brother had whooping cough when they were six and five years old. Her heart started enlarging

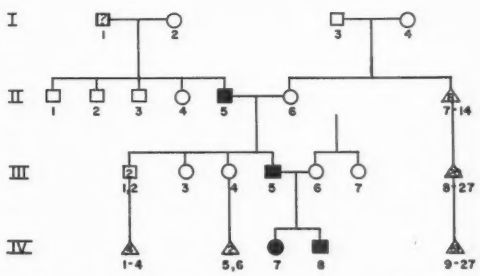


FIG. 10. The pedigree of a family in which Marfan's disease may have occurred in four successive generations with a striking history of aortic complications. The squares indicate males and the circles females. The inked-in symbols indicate definitely affected persons.

at that time. She was extremely nearsighted and wore glasses from the age of three years. She had a bad spinal curvature that we first noticed when she was ten. The family doctor did not advise a brace or cast as she was so frail and her heart was getting increasingly worse. During her last illness which lasted six weeks, the doctor said that her heart was just as it would have been in a person in his forties who had had rheumatic fever in his youth, that her heart was just worn out. She died at the age of 12½ years and was 5 feet 2 inches tall in spite of a very bad curvature. She had a brilliant mind and was at the top of classes in spite of her many handicaps. Both of the children were thin to the point of looking emaciated."

The brother of this girl (IV-8) "was born Nov. 27, 1938. He and Catharine looked like twins and were as nearly like their father as was possible. He was well as a baby and up to the time that he had whooping cough at the age of five. After that long siege of coughing, the doctor discovered that he had a heart murmur. His heart enlarged so that his chest protruded. He complained of chest pain occasionally. He died suddenly in August 1946. His sister said after he died that he had complained of severe chest pains a couple of days before but he didn't tell anyone else. He developed hernia when he was about two years old but it never seemed to bother him. He had a bad case of influenza the winter before he died and had a bad cough that lingered all winter and we felt hastened his death."

At age 7 this patient was 53 inches tall and weighed 51 pounds. He showed arachnodactyly, hypotonia, hammer toes, thin and translucent skin, ectopia lentium, cardiomegaly, dilatation of the aorta, aortic systolic and diastolic murmurs, left axis deviation (by electrocardiogram), deformity (not described in detail) of the hip joints and skull (by x-ray examination). The lenses in this case were misplaced downward and outward.

General Comments

It must be emphasized that the principal cardiovascular component of Marfan's syndrome, the abnormality of the aorta, is not in the true sense "congenital heart disease" or a "congenital malformation". It is comparable to the abiotrophies of the neurologists: the weakness is present at birth, although perhaps not recognizable by ordinary histologic technic, it expresses itself only later in extra-uterine life, often very late.

It has been suggested by several writers that many cases of so-called Erdheim's cystic medial necrosis with dissecting aneurysm are not apparent instances of Marfan's syndrome. Other factors than hypertension must certainly play a role in dissecting aneurysm since there is a significant proportion of occurrences in normotensive individuals. Furthermore, experience at this hospital and elsewhere[31, 32] is that 20 to 25 per cent of cases of dissecting aneurysm occur in persons under 40 years of age. Frei[33] encountered this lesion in a 14 month old individual and in a boy of 10 years. Erdheim's cystic medial necrosis has been observed to produce diffuse aortic dilatation in a patient who was not noted to have the stigmata of Marfan's syndrome.[34] It seems possible that the morphologic entity which Erdheim described may not be a homogeneous entity etiologically but may, in individual instances, have various pathogeneses, hereditary and acquired. One of these causes is the hereditary connective tissue defect of Marfan's syndrome. The connective tissue defect of Ehlers-Danlos syndrome may be a second hereditary cause (see below).

Although what element of connective tissue is primarily defective in Marfan's syndrome is unknown, there are some reasons to suspect that it is the elastic fiber or an element intimately related to the elastic fiber. From the end-stage findings in a case such as that illustrated by figure 5 a to d, it is difficult to reconstruct the chain of pathogenetic events. However, one seemingly plausible reconstruction interprets the disruption of the elastic lamellae as primary. Then the smooth muscle fibers which normally have their origin and insertion on the elastic plates collapse together and apparently undergo pronounced hypertrophy and hyperplasia, possibly as a compensatory mechanism. The increased vascularization of the aortic media may be a response to these changes in the smooth muscle.

The production in rats of a somewhat analogous, but *acquired*, syndrome has been of great interest for obvious reasons. Kyphoscoliosis, hernia and either dissecting, diffuse, or saccular aneurysm of the aorta are produced by the feeding of a toxic agent contained in the seed of *Lathyrus odoratus*.[35, 36] Although there are reasons to believe that the basic defects are *not* identical in these two syndromes, experimental studies such as this may provide a lead on the inborn metabolic aberrations which are the basis of the morphologic abnormality of the aorta in Marfan's syndrome and on the acquired aberration in the case of "metabolic" dissecting aneurysm such as that which may occur during pregnancy[31] and with hypothyroidism.[37]

My data indicate that approximately 15 per cent of all cases occur as a result of *de novo* mutation. In the remaining instances, the victim was a descendant of such an original case or descended in a line with Marfan's syndrome present in each generation as far back as it was possible to trace. Once having occurred by mutation in a family line, the Marfan trait is inherited as a dominant.

About 80 per cent of the cases have ectopia lentis. When ectopia lentis was absent it was frequently difficult to be certain about the diagnosis of Marfan's disease. On the other hand, the other stigmata of Marfan's syndrome may be so subtle that for practical purposes it is probably safer to consider all cases of ectopia lentis potential victims of the aortic complications here discussed. This is assuming, of course, that the ectopia lentis is not clearly part of some other syndrome such as that of Weill and Marchesani[38, 39] in which the victim shows striking brachymorphism rather than the dolichomorphism of Marfan's syndrome (fig. 11).

In the differential diagnosis of Marfan's

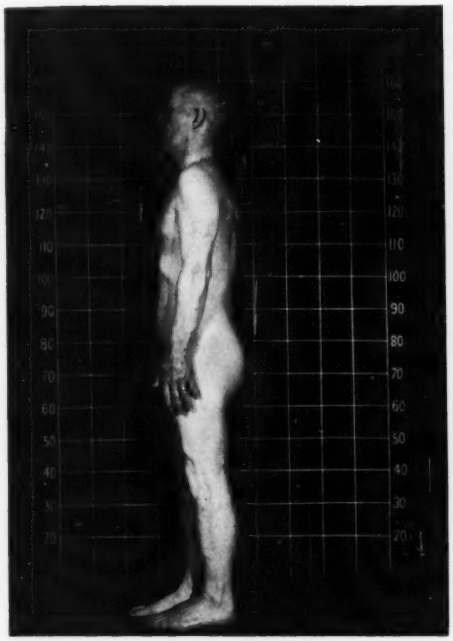


FIG. 11 A

FIG. 11 B

FIG. 11 A and B. Shown here are father and daughter with the Weill-Marchesani syndrome (ectopia lentis and brachymorphism). The skeletal manifestations are the antithesis of those of Marfan's syndrome. The daughter has a cleft palate and is mentally defective. No definite cardiovascular abnormality has been identified in cases of this syndrome. Compare these father-daughter pictures with that in figure 3 A.

disease the malformations resulting from Rh incompatibility and from maternal rubella are important. Mother-child blood typing and the history may aid in the differential. Given a case with skeletal proportions consistent with Marfan's disease and a complication, such as aortic regurgitation, which might be on that basis, it is virtually impossible to be completely certain whether Marfan's disease is actually present unless 1—ectopia lentis, the least equivocal component of the syndrome, is also present or 2—unequivocal instances of the syndrome are represented by other members of the family. In the Negro, in particular, a habitus confusingly suggestive of Marfan's syndrome is frequently met. Some of these are a *forme fruste* of the syndrome; most of them are merely anthropologic variants. (For example, one famous contemporary Negro basketball star has a height of 75½ inches and an arm span of 84 to 86 inches.) Eunuchism and sickle cell disease are two pathologic conditions which are accompanied by skeletal changes like those of Marfan's disease.

Currently under study are two other hereditary disorders of connective tissue in which cardiovascular involvement occurs. One, pseudoxanthoma elasticum, is clearly a systemic dystrophy, probably of collagen[40] rather than elastic fibers, with important generalized arterial involvement.[41, 42] In the other condition, Ehlers-Danlos syndrome (hyperelastica cutis), the evidence of cardiovascular involvement is much less conclusive although associated congenital malformations of the heart, specifically interatrial septal defect[43] and tetralogy of Fallot[44], have been reported in individual patients with this last syndrome. I have encountered one patient with Ehlers-Danlos syndrome who succumbed to dissecting

aneurysm of the aorta. In this patient, a 27 year old white man, dissection began in the renal artery producing retroperitoneal hematoma and leading to laparotomy.

Summario in Interlingua

Del puncto de vista clinic le morbo de Marfan se presenta como un abiotrophia de alicun elemento del texitos conjunctive. Su manifestationes cardiovascular resulta de defective medios aortic, de defective cuspides valvular, de communicationes interatrial, e de pectore excavate. Le defecto del medios aortic se manifesta per aneurysma dissecante, per aneurysma diffuse del aorta ascendente, e per un combination de ambes. Nos presenta un description de subacute endocarditis bacterial in un patiente con morbo de Marfan. Defectos del septo interatrial es minus frequente que previemente supponite. Symptomas cardiac in sever casos de pectore excavate debe esser evalutate in consideration del possibile presentia de morbo de Marfan. Nos ha colligite datos ab cinquanta familias in qui occurreva al minus un caso indubitabile de morbo de Marfan.

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The Treatment of Acute Rheumatic Fever in Children

A Cooperative Clinical Trial of ACTH, Cortisone and Aspirin

A joint report by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.*

Members of the Rheumatic Fever Working Party and United Kingdom participating centers: The late Sir James Spence (Chairman), Royal Victoria Infirmary, Newcastle; Professor A. Bradford Hill, Honorary Director, Statistical Research Unit of the Medical Research Council (Vice-chairman, and Chairman following the death of Sir James Spence); Dr. E. G. L. Bywaters (Secretary), Canadian Red Cross Memorial Hospital, Taplow; Professor Stanley Graham, Royal Hospital for Sick Children, Glasgow; Professor R. S. Illingworth, The Children's Hospital, Sheffield; Dr. B. E. Schlesinger, Hospital for Sick Children, Great Ormond Street, London; Professor A. G. Watkins, Llandough Hospital, Cardiff.

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Associated investigators at cooperating centers: In the United Kingdom: Drs. O. P. Gray and J. Rendle-Short, Cardiff; Drs. Gavin C. Arneil and James Hutchison, Glasgow; Drs. J. Greaves and R. G. Welch, London; Dr. E. Ellis, Newcastle; Drs. S. Doxiadis and M. G. Philpott, Sheffield; Dr. G. T. Thomas, Taplow. In the United States: Drs. John Bray and Ernest Craige, Boston; Drs. Ernest Clark and Harold B. Houser, Cheyenne; Drs. Andrew Lorincz, Irving Rozenfeld and Katherine Smull, Chicago; Drs. James Flett, Jr. and John H. Githens, Denver; Drs. Felix E. Demartini and Charles W. Frank (Columbia) New York; Drs. Frances L. Bailen-Rose, Janet Baldwin, Joseph J. Bunim, Eugenia F. Doyle, Ann Kuttner, Gene H. Stollerman and Morris Ziff (New York University) New York; Drs. A. D. McKelvey and Richard Rowe, Toronto (Canada).

Statistical consultation and services were provided by Miss Marjorie T. Bellows, Chief Statistician of the American Heart Association and Dr. John Knowelden, London School of Hygiene and Tropical Medicine. Mr. Felix Moore, Chief, Biometrics Research Branch, National Heart Institute served as statistical consultant. Dr. A. St. J. Dixon, Taplow, served as Coordinating Registrar for the British centers. Mrs. Ruth E. Rutstein was Coordinator for the centers in the United States.

The National Heart Institute of the United States Public Health Service supported the study with grants to the coordinating center and to the cooperating centers in the United States and by a travel grant to the Medical Research Council of Great Britain. The Medical Research Council provided support for the six centers and for a coordinating registrar in the United Kingdom. The center in Toronto received a grant from the Canadian Arthritis and Rheumatism Society. In the United States, the costs of the medical care of its patients were met by each cooperating center, and in Great Britain by the National Health Service. The American Heart Association provided office space for the American Coordinating Center and a grant for statistical services.

This cooperative clinical trial was first proposed by Dr. John R. Mote, then assistant general manager of the Armour Laboratories. For the planning of the study, funds were provided by Armour Laboratories and Merck and Company, and space and services by the Helen Hay Whitney Foundation.

In the planning and conduct of this trial much is owed to the wise advice and guidance of the late Dr. T. Duckett Jones and the late Sir James Spence.

* This report is being published simultaneously in the BRITISH MEDICAL JOURNAL in the United Kingdom and in CIRCULATION in the United States.

STARTING in 1949, encouraging reports of ACTH* and cortisone in the treatment of acute rheumatic fever aroused hope that a more effective therapy had at last become available. Conclusions of the early and uncontrolled studies were, however, somewhat contradictory, in that some investigators reported that the hormones altered the course of acute rheumatic fever while others suggested that they merely suppressed its clinical manifestations (see bibliographies in Thorn[1] and Massell[2]). At that time, no data were available concerning the prevention of rheumatic heart disease by these agents, a question which could be answered only by a long follow-up study.

By early 1950, it became evident to both the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association and the Medical Research Council of Great Britain that there was a need for a controlled study of the efficacy of these hormones in comparison with the previously accepted therapy. It was also clear that no single research center could provide in a short period of time, enough cases to give a definitive answer. It was therefore proposed that a group of research centers should collaborate. The cooperative clinical trials of the streptomycin treatment of tuberculosis in Great Britain under the Medical Research Council and of similar studies in the United States under the Veterans Administration pointed the way. Planning funds were soon made available.

There were several advantages in the establishment of a cooperative study on an international basis. It was possible that the general availability of ACTH and cortisone in the United States might seriously interfere with a strictly controlled clinical trial. Large numbers of cases would be collected rapidly. Much needed information on the natural history of the disease in two different parts of the world would be made available.

The Committee on Criteria and Standards of the Council on Rheumatic Fever and Congenital Heart Disease, together with a group of American and Canadian rheumatic fever research workers, set up a subcommittee of principal investigators for American planning. It also established liaison with the Working Party on Rheumatic Fever of the Medical Research Council of Great Britain. Joint planning of the United Kingdom-United States Cooperative Rheumatic Fever Study was begun and the design of the study completed in a six month period.

The trial was designed to compare the therapeutic effects of the hormones, ACTH and cortisone, with the usual treatment of rheumatic fever at the time, viz., aspirin, all patients to be treated in hospital or bed rest and protected against beta hemolytic streptococcal infection. Within the limitations imposed by the design of the study, answers were sought to two questions:

1.—What is the relative effectiveness of each of these hormones and of aspirin in altering the course of the acute disease or in suppressing its clinical manifestations?

2.—What is the relative effectiveness of these three agents in preventing rheumatic heart disease?

Information was also collected on the side effects of the two hormones and of aspirin.

The design created and agreed upon by the principal investigators in both countries, in cooperation with the coordinating staff and statistical consultants, provided for diagnostic criteria, random allocation of patients to treatment groups, a uniform six-week therapeutic regimen and a fixed time pattern for observation and follow-up. It prescribed the type and frequency of clinical and laboratory observations during hospital stay and follow-up period and required reporting on specially prepared forms (Appendix) to the coordinating centers in London and New York City.

This report compares the effects of the three drugs—ACTH, cortisone and aspirin—on the acute course of rheumatic fever in children under the age of 16, through 13 weeks from the start of treatment, and on the persistence and development of rheumatic heart disease through one year.* Subsequent reports will

* Throughout this paper, ACTH will be used to indicate corticotropin, N.N.R.

* The one year follow-up data represent observations made at a calendar year from the end of the nine-week period of treatment and observation (61 weeks from the start of therapy).

include a similar analysis of adult patients and, after longer follow-up, of the relative effectiveness of the three drugs in the prevention of rheumatic heart disease. These extensive data should also provide much information on the natural history of the disease.

Diagnostic Criteria for Admission of a Patient to the Study

To insure, as far as possible, that in all centers patients admitted to the trial were unquestionable cases of rheumatic fever, and of no other illness, it was necessary to specify precise diagnostic criteria. Since there are no specific diagnostic clinical symptoms or signs or laboratory tests, such criteria must be arbitrary. The criteria had to be broad enough not to exclude many genuine early cases, and yet sufficiently rigid that there should be, among competent clinicians, no reasonable doubt regarding the diagnosis.

The diagnostic criteria were based on those of T. Duckett Jones,[3] modified for the purposes of this study with his advice and assistance.* They divide the manifestations of rheumatic fever into two groups, major and minor. There were five major manifestations, defined as follows:

Major Manifestations

1. *CARDITIS* as shown by any one of the following:
   (a) *Development of an organic apical systolic murmur or an aortic diastolic murmur under acceptable observation.*†
   (b) *Change of heart size of more than 15 per cent on standard x-ray film by any standard method of measurement.*
   (c) *Pericarditis revealed by a definite friction rub or by pericardial effusion.*
   (d) *Congestive failure, in a patient under 25 years and in the absence of other causes, and shown by one or more of the following: (1) dyspnea, (2) orthopnea, (3) enlargement of the liver, (4) basal pulmonary rales, (5) increased jugular venous pressure or (6) edema.*

   In the assessment of carditis as a criterion for entry to the trial, it was assumed in patients with no known pre-existing rheumatic heart disease or history of an attack of acute rheumatic fever, that previous to the current illness the patient's heart was of normal size and that there were no rheumatic murmurs. In other patients, observations of changes in heart size and murmurs were used in determining carditis, and recorded.
2. *POLYARTHRITIS as shown by pain and either limitation of active motion or tenderness, in two or more joints.*
3. *CHOREA with movements of at least moderate severity.*
4. *SUBCUTANEOUS NODULES.*
5. *ERYTHEMA MARGINATUM* (or *ANNULARE*).

The minor manifestations also numbered five and were as follows:

Minor Manifestations

1. *FEVER defined as any temperature above 99.3 F. (37.4 C.) by mouth or 100.3 F. (38 C.) rectally, occurring at least twice in one period of 24 hours, or above 100.3 F. (38 C.) by mouth or 101.3 F. (38.5 C.) rectally, observed on any one occasion.*
2. *ELEVATED SEDIMENTATION RATE defined as 15 mm. in 1 hour or above (Wintrobe, corrected by the Whitby and Hines chart to a hematocrit of 45 per cent).*
3. *EVIDENCE OF PREVIOUS STREPTOCOCCAL INFECTION as shown by a culture in which beta hemolytic streptococcus predominated, or by an antistreptolysin O titer of 200 units or greater, or by a reliable history of sore throat with fever preceding the onset of illness by an interval of one week to one month.*
4. *AN INCREASED P-R INTERVAL defined as a value at least 0.04 second beyond those given in the Ashman-Hull[4] tables for ages under 16.*
5. *A RELIABLE HISTORY OF RHEUMATIC FEVER as defined in these criteria or EVIDENCE OF PRE-EXISTING RHEUMATIC HEART DISEASE (viz., an apical organic systolic murmur, an apical diastolic or a basal diastolic murmur).*

These criteria having been specified, it was ruled that to be admitted to the study, the patient must (a) at some time during the illness which brought him to the center, have exhibited at least two major manifestations *or* one major and two minor manifestations, and (b) on the first day of the allotted therapy, show evidence of any one major manifestation *or* of any two of the three following minor manifestations: fever, elevated sedimentation rate, increased P-R interval.

It was arbitrarily decided that an interval of at least three months with no rheumatic activity must have preceded the present illness to justify its being called a new attack. With any shorter interval of time between the present and a previous illness, the present illness was held to be an exacerbation of symptoms of the previous attack and not a new

* These modified criteria are not necessarily applicable for general use by the practicing physician, particularly in questionable cases where continued observation of patients may be necessary for definitive diagnosis.

† The development of an apical mid-diastolic murmur was also used for the diagnosis of carditis in U. K. centers, but there was only one case in which the diagnosis of carditis rested solely on this murmur, and this case was eligible under other criteria.

attack. In such instances, the date of onset was referred back to the beginning of the illness.*

Patients who had had previous hormone therapy were excluded from the trial (a single test dose previously administered was not regarded as therapy). If a patient was receiving salicylate therapy, that treatment was discontinued upon admission to the hospital before the patient was considered for inclusion. If such a patient subsequently satisfied the criteria, he was eligible and admitted in the ordinary way.

Treatment Plan

Dosage Schedules

The dosage schedules of ACTH, cortisone and aspirin were based (in 1950) on published studies, modified by reports from investigators to Armour Laboratories and Merck and Company. From such information, a dosage was selected to be effective for a period of administration short enough to indicate whether the acute attack had been differentially shortened by any one of the three drugs. Provision was made for decreasing the dosage if toxic manifestations appeared and for "tapering off" so that cessation of therapy would not be abrupt.

While the same hormone dosage was used for all patients, the dosage schedule of aspirin was calculated on the basis of body weight. Cortisone and ACTH were administered intramuscularly, while aspirin was given by mouth.

The dosage schedules were:

ACTH.† All cases U. K. and eight cases U. S.:‡ a total daily dosage of 80 USP units for the first four days, 60 units for the next three days, 40 units for the second and third weeks, 30 units for the fourth and fifth weeks and 20 units for the sixth week, administered every six hours.

All but eight cases U. S.: a total daily dosage of 120 USP units for the first four days, 100 units for the next three days, 80 units for the second week, 60 units for the third week, 40 units for the fourth and fifth weeks, 20 units for the sixth week, administered every six hours.

The ACTH dosage in the U. S. was increased early in the study, because with the relatively poor methods available for lot standardization and the lack of dramatic response in the first few cases treated, it was held possible that optimum dosage was not being administered. In regard to the question of "adequacy" of hormone dosage, it is of interest that practically all cases receiving ACTH or cortisone had side effects, the details of which are presented later.

*Cortisone.** A total daily dosage of 300 mg. for the first day, 200 mg. for the next four days, 100 mg. for the remainder of the first three weeks, 75 mg. for the fourth and fifth weeks, 50 mg. for the sixth week.

In the few cases where the hormone dosage was reduced because of undesirable side effects, the percentage stepwise reduction in dosage thereafter remained unchanged.

Aspirin (acetylsalicylic acid, USP or BP, 0.3 Gm. (5 grain) tablets). A total daily dosage of 60 mg. (1 grain) per pound of body weight or 10 Gm. (150 grains) total dosage, whichever was less, for the first two days, 40 mg. (⅔ grain) per pound, or 10 Gm. (150 grains), whichever was less, for the next five days, 30 mg. (½ grain) per pound for the remainder of the six weeks. (Administered every four hours for 48 hours, every six hours thereafter.) Aspirin was administered without bicarbonate of soda.

Patients unable to tolerate aspirin in the scheduled dosage received the largest amounts that they could tolerate as determined by the investigator. This occurred mainly in the older patients where the body weight dosage produced side effects. Conversely, because of the weight dosage formula, small children did not receive aspirin up to the limit of tolerance.†

During the three week observation period following the six week course of therapy, none of these drugs was administered unless the investigator believed that the patient's condition was so poor as to endanger life or the polyarthritis so painful that it could not otherwise be controlled. In such cases, retreatment was given for a period of four weeks, using the same drug and dosage as in the

* "Onset" was defined as the date of the first observation of any major manifestation or any minor manifestation that appeared to be related in a continuous time sequence to the development of any major manifestation.

† ACTH donated by Armour Laboratories was in three lots of water-soluble material standardized on both animals and human beings. All the U. K. cases were treated with one lot (K-50601R), while most of the U. S. cases received a second lot (J-24109R), although a few were treated with a third lot (L-56702). The USP unit is expressed as a milligram equivalent of ACTH lot number LA-IA.

‡ One Canadian center took part in the trial, but for easy reference, the term "U. S." is used to include all North American centers.

* Cortisone donated by Merck and Company was the regular commercial preparation for intramuscular use, namely the acetate of 17-hydroxy-11-dehydrocorticosterone, suspended in a vehicle consisting of sodium carboxymethyl cellulose, Tween 80, and 1.5 percent benzyl alcohol in isotonic saline.

† Salicylate blood levels determined in two U. S. centers showed a positive correlation with body weight; lower blood levels found in one U. K. center revealed no such relationship.

f st four weeks of initial therapy; it was followed l · a three week observation period as before.

If retreatment was necessary at any time during t e three months following the original course of t erapy, then the above four week retreatment s heme was followed. No patient was retreated u less he demonstrated rheumatic activity sufficient t have brought him into the study initially.

If, after three months without activity, the pa- t ent developed a new attack of rheumatic fever, l e was treated as in the original course, i.e., for s x weeks on the same drug and dosage, followed by a three week period of observation.

Auxiliary Therapy

Sodium and Potassium Intake. To minimize salt retention in hormone treated patients, and to maintain comparability among the three treatment groups, the dietary intake of sodium was restricted to less than 2 Gm. per day for all patients for at least four weeks. All patients received added potassium chloride by mouth daily, 2 Gm. for those weighing less than 60 pounds and 3 Gm. for those 60 pounds or more, except that those few who developed oliguria due to congestive failure received no added potassium. Serum potassium levels were estimated weekly.

Streptococcal Prophylaxis. Every effort was made through streptococcal prophylaxis to prevent recurrent attacks of rheumatic fever which would introduce an additional variable in the study. All patients, upon admission to the study and on the fourth, seventh and tenth day of treatment, received procaine penicillin G in aluminum monostearate intramuscularly, 300,000 units for those weighing less than 60 pounds, 600,000 units for those weighing 60 pounds or more.* On the fourteenth day after admission to the study, and continuously thereafter, sulfadiazine was administered in a dose of 0.5 Gm. per day to those weighing less than 60 pounds and 1 Gm. per day to those weighing 60 pounds or more. (In a few patients, oral penicillin in a dose of 100,000 units, twice a day, was substituted when sensitivity to sulfadiazine developed.) Sera were drawn for determination of antistreptolysin-O titers[5] at weeks 0, 5, 9 and 13, and at each follow-up examination, to detect intercurrent streptococcal infection.

In addition to this routine, throat cultures were made on all patients on admission to the hospital, and thereafter whenever there was indication of a throat infection. Those with positive cultures received penicillin therapy, as prescribed by the investigator.

Other Therapy. All but a few patients were kept at bed rest for the nine weeks of therapy and observation. In a few cases of chorea, sedatives were necessary. No antirheumatic drugs other than those allocated for the study were given. Therapy necessary for any complicating illness was recorded.

* At the House of the Good Samaritan, Boston, variable dosage schedule was used.

The Allocation of Patients to Treatment

Patients on admission to the study were divided into two age groups, 0 to 15 years and 16 and over, and into three groups according to the length of time in each case between the date of onset of the attack and the date at which therapy began. The three duration-from-onset groups were (1) 14 days or less; (2) 15 to 42 days; (3) 43 days and over.

For each of these three duration groups, within each age group, and separately for each treatment center, the three treatments, ACTH, cortisone and aspirin, were listed in random order for as many patients as were likely to be admitted, using random sampling numbers and keeping the numbers of patients on the three treatments approximately equal in each center. The coordinating center in each country issued serially numbered and sealed envelopes to the treatment centers. Thus, on admission of a patient of given age and specified duration-from-onset group, the investigator at the treatment center had merely to open the next available envelope for that particular group to find a statement of the treatment to be applied. He was, therefore, unable to predict the treatment for his next case. The allocation was both "blind" and random.*

The admission report on the patient, and the assignment envelope, were then sent to the coordinating center. If, for any special reason, the investigator decided in advance that a patient fulfilling the criteria should not be admitted to the study, no envelope was opened. In every such case, however, an admission report was required, together with an explanation as to why the patient had not been admitted. Six such cases were reported in the U. S.; none in the U. K.†

* In a few centers, for varying durations of time, the investigators wished to withhold some patients for other studies. In these instances a predetermined proportion of the envelopes contained, as an instruction, "free case." Such exclusions, therefore, were also "blind" and randomly determined and could not bias the group brought into the study.

† These six cases were: one, with schizoid personality, considered unsuitable for the trial; one, excluded because his private physician insisted upon cortisone therapy; and four severe cases excluded in one center under provision of the protocol (viz., "If in the opinion of the principal investigator, the patient is severely ill to the point where his life is in danger, that patient may be removed from any group and given therapy at the discretion of the investigator.") These four cases were treated with ACTH as follows: (1) a 12 year old boy in a sixth attack with acute carditis, mitral insufficiency and

TABLE 1.—*Details of 15 Cases Admitted to the Study in Which the Treatment and Observation Schedule Was Not Followed, with Reference to Their Inclusion or Exclusion from the Analysis*

Treatment Group	Treatment Stopped (5 cases)	Treatment Changed (5 cases)	Retreatment (4 cases)	Treatment Incomplete (1 case)
ACTH (4 cases)	(1) U. S. Gastric hemorrhage 6th day. Excluded (2) U. S. Renal hemorrhage 21st day. Included. (3) U. S. Toxicity* 27th day. Included. (4) U. K. Toxicity† 32nd day. Included.			
Cortisone (3 cases)			(11) U. S. Retreated 48th day. Included. (12) U. S. Retreated 50th day. Included.	(15) U. S. Patient left hospital 12th day.‡ Excluded.
Aspirin (8 cases)	(5) U. S. Discharged from hospital 41st day.§ Included.	(6) U. S. In failure. Changed to ACTH 8th day. Excluded. (7) U. S. Carditis and failure. Changed to ACTH 28th day. Included under aspirin. (8) U. S. Carditis. Changed to ACTH 28th day. Included under aspirin (9) U. S. Carditis. Changed to cortisone 50th day. Included under aspirin. (10) U. K. Pericarditis and failure. Changed to cortisone 51st day. Included under aspirin.	(13) U. S. Retreated 45th day. Included. (14) U. S. Retreated. 58th day. Included.	

* Unusually rapid weight gain and enlargement of liver not responding to mercurial diuretics.
† Too rapid development of moonface.
‡ Family moved to another city.
§ Child was an unmanageable behavior problem.

THE STUDY SAMPLE

In all, 505 children under 16 years of age were admitted to the study, 242 in the U. K. between March 2, 1951 and Oct. 6, 1952, and 263 in the U. S. between Jan. 15, 1951 and June 15, 1952. Four of these cases were subsequently excluded when their illness proved to be a disease other than rheumatic fever. These were a case on cortisone (U. K.) of Henoch-Schonlein purpura, a case on aspirin (U. K.) of tuberculous meningitis, a case on ACTH (U. S.) of lupus erythematosus disseminatus, and a case on ACTH (U. S.) of salmonella infection. In another case on ACTH (U. S.) there was x-ray evidence of tuberculous infection superimposed upon the rheumatic fever, and hormone treatment was therefore withheld. These five exclusions present no problem.

In the remaining 500 patients (240 U. K., 260 U. S.), there was only the small number of 15, or 3.0 per cent, in whom the prescribed treatment and observation schedule was not fully carried out (2 U. K., 13 U. S.). Table 1 shows their nature and

congestive failure, made a smooth recovery without residual heart disease; (2) a nine year old girl in a second attack with residual heart disease, mitral insufficiency and congestive failure made a gradual but unremarkable recovery; (3) a 12 year old girl in a second attack, with residual heart disease, acute carditis, mitral insufficiency and congestive failure, made, after a stormy course, a slow recovery with persistence of chronic heart disease with increasing cardiac enlargement; and (4) a nine year old boy in a first attack with mitral insufficiency, pericarditis and congestive failure, died after seven days of treatment.

he action taken with regard to them. Only three Cases 1, 6 and 15) have been wholly excluded from he statistical analysis of the trial, since their treatnent with the allotted drug was very brief (6, 8 nd 12 days). All other cases had been treated for hree weeks or longer. Three of them (cases 2, 3 nd 4) fall within the original provision for a reduction of dosage when essential, and four (cases 11, 2, 13 and 14) within the provisions for retreatment n active cases. Such patients, together with one case 5) that left the hospital after the six weeks of herapy, can be included under the allotted therapy vithout any difficulty.

There remain four aspirin cases in which on ccount of the severity of the illness, the investigator administered hormone treatment. In two (cases 7 and 8), a change to ACTH was made during the treatment period (on the twenty-eighth day); in two, treatment with cortisone was instituted during the observation period (on the fiftieth and fifty-first days), after completion of the aspirin treatment. It was thought better to continue these cases in the aspirin group in spite of the change of treatment since the exclusion of these four cases from the analysis at these points of time would make the picture of the aspirin group somewhat too favorable, since severely ill cases were being artificially removed from it.

Altogether, it is clear that these three exclusions, four changes of the allotted treatment and eight variations of the treatment schedule can have had no appreciable effect upon the results of the trial.

Two U. S. and four U. K. patients died during the first year and are included in the analysis.

Taken as a whole, the 497 cases under age 16 show the following features. There were altogether, 14 cases [3 per cent] aged 3 or 4 years, 200 [40 per cent] aged 5 to 9 years and 283 [57 per cent] aged 10 to 15 years. In just over one-half (255), the allotted therapy was begun within 14 days of the onset of the attack and a more detailed analysis shows that 149 or 60 per cent of these "early" cases were treated within one week of onset. In nearly two-thirds (327 cases) there was neither history of a previous attack of rheumatic fever nor evidence of pre-existing rheumatic heart disease. Only 128, or approximately one-fourth, of the 497 cases were in fact definitely diagnosed as having pre-existing rheumatic heart disease at the start of therapy. Mitral stenosis as shown by an apical presystolic murmur was reported in only 16 cases. In general, therefore, the group contained a large proportion of cases still in the early stages of the disease.

The Comparability of the Treatment Groups at the Start of Therapy

The method of allocation insured that in each treatment group there was approximately the same number of cases with regard to the duration from onset of attack to start of therapy. Thus, there were in ACTH, cortisone and aspirin, respectively, 86, 85 and 84 "early" cases (0 to 14 days); 47, 45 and 46 "medium" cases (15 to 42 days); and 29, 37 and 38 "late" cases (43 days or more) (table 2). The average age and mean body weight in the three treatment groups were almost identical and the sex distribution was reasonably alike. In general, it is clear that the balance produced by the design of the study permits amalgamation of the duration-from-onset groups and of the data for the two countries.

TABLE 2.—*Comparison of Treatment Groups at Start of Therapy: Duration of Illness from Onset, Sex, Mean Age and Mean Weight*

Treatment Group	Total Cases	Duration from Onset			Sex		Mean Age (years)	Mean Weight (pounds)
		0–14 days	15–42 days	43+ days	M	F		
U. K.								
ACTH.....	80	39	27	14	40	40	10.0	66.0
Cortisone...	80	38	25	17	34	46	9.9	63.6
Aspirin.....	80	32	27	21	40	40	9.6	64.4
Total.....	240	109	79	52	114	126	9.8	64.7
U. S.								
ACTH.....	82	47	20	15	51	31	9.9	71.4
Cortisone...	87	47	20	20	45	42	10.1	71.7
Aspirin.....	88	52	19	17	49	39	10.2	73.6
Total.....	257	146	59	52	145	112	10.1	72.2
U. K. & U. S.								
ACTH.....	162	86	47	29	91	71	10.0	68.8
Cortisone...	167	85	45	37	79	88	10.0	67.9
Aspirin.....	168	84	46	38	89	79	9.9	69.2
Total.....	497	255	138	104	259	238	10.0	68.6

Clinical features of the three treatment groups at the start of therapy are compared in table 3. With regard to the first item, temperature, it should be noted that oral temperatures were taken in the U. K. (except at one center) and rectal temperatures in the U. S. (except at one center). An arbitrary correction of each oral reading was made by the addition of 1 F., and the tabulations are of the maximum "rectal temperature" recorded on each day. As the distribution of patients in each center was evenly divided among the three treatment groups, the comparison between treatments should not be biased, even though the arbitrary temperature correction may be imperfect. It will be seen that at the start of therapy, there was a larger proportion of U. S. cases (57.6 per cent) with a rectal temperature of 100.4 F. or above, than of U. K. cases (45.4 per cent). This difference may be real but it is possible that the addition of 1 F. to the oral temperature may not make the latter en-

TABLE 3.—*Comparison of Treatment Groups at Start of Therapy: Percentage with Specified Symptoms*

		Treatment Group			Total
		ACTH	Cortisone	Aspirin	
Number of cases	U. K.	80	80	80	240
	U. S.	82	87	88	257
	U. K. & U. S.	162	167	168	497
Temperature 100.4 F. or more (rectal)	U. K.	47.5	51.2	37.5	45.4
	U. S.	59.8	70.1	43.2	57.6
	U. K. & U. S.	53.7	61.1	40.5	51.7
Pulse during sleep 100 or more per minute	U. K.	41.8	33.3	34.6	36.6
	U. S.	29.2	36.0	26.1	30.6
	U. K. & U. S.	35.8	34.6	30.6	33.7
ESR 20 mm or more in 1 hr.	U. K.	87.5	86.2	88.8	87.5
	U. S.	96.3	93.8	94.1	94.7
	U. K. & U. S.	91.9	90.0	91.5	91.2
Joint involvement	U. K.	33.8	36.2	40.0	36.7
	U. S.	43.9	56.3	47.7	49.4
	U. K. & U. S.	38.9	46.7	44.0	43.3
Subcutaneous nodules	U. K.	22.5	23.8	18.8	21.7
	U. S.	9.8	6.9	5.7	7.4
	U. K. & U. S.	16.0	15.0	11.9	14.3
Chorea	U. K.	8.8	13.8	22.5	15.0
	U. S.	2.4	9.2	9.1	7.0
	U. K. & U. S.	5.6	11.4	15.5	10.9
Erythema marginatum	U. K.	10.0	8.8	5.0	7.9
	U. S.	4.9	4.6	2.3	3.9
	U. K. & U. S.	7.4	6.6	3.6	5.8
Pre-existing rheumatic heart disease	U. K.	31.2	32.5	31.2	31.7
	U. S.	28.0	14.9	18.2	20.2
	U. K. & U. S.	29.6	23.4	24.4	25.8
Pericarditis	U. K.	10.0	16.2	5.0	10.4
	U. S.	6.1	3.4	5.7	5.1
	U. K. & U. S.	8.0	9.6	5.4	7.6
Congestive failure	U. K.	12.5	10.0	3.8	8.8
	U. S.	15.9	8.0	8.0	10.5
	U. K. & U. S.	14.2	9.0	6.0	9.7
Cardiothoracic ratio of 0.55 or more	U. K.	21.5	26.0	13.3	20.3
	U. S.	22.5	11.8	10.5	14.7
	U. K. & U. S.	22.0	18.5	11.8	17.4
Atrioventricular conduction time of 0.18 sec. or more	U. K.	32.5	30.1	24.4	28.9
	U. S.	34.2	38.3	32.1	34.9
	U. K. & U. S.	33.3	34.4	28.3	32.0
No organic murmur	U. K.	20.0	13.8	17.5	17.1
	U. S.	26.8	33.3	36.4	32.3
	U. K. & U. S.	23.5	24.0	27.4	24.9
Apical systolic murmur	U. K.	75.0	77.5	73.8	75.4
	U. S.	69.5	64.4	59.1	64.2
	U. K. & U. S.	72.2	70.7	66.1	69.6
Apical mid-diastolic murmur	U. K.	48.8	46.2	45.0	46.7
	U. S.	34.1	23.0	25.0	27.2
	U. K. & U. S.	41.4	34.1	34.5	36.6
Basal diastolic murmur	U. K.	38.8	35.0	33.8	35.8
	U. S.	12.2	12.6	11.4	12.1
	U. K. & U. S.	25.3	23.4	22.0	23.5
Apical presystolic murmur	U. K.	5.0	2.5	1.3	2.9
	U. S.	4.9	3.4	2.3	3.5
	U. K. & U. S.	4.9	3.0	1.8	3.2

tirely equivalent to the rectal temperatures taken in the U. S.

The proportion of cases initially febrile (those with a temperature of 100.4 F or greater) among the three treatment groups is dependent upon whether comparison is made on the first day of treatment or on the day before treatment was begun. On the first day of treatment, there was a smaller proportion of cases febrile in the aspirin group (40.5 per cent) than in the cortisone (61.1 per cent) or the ACTH (53.7 per cent) groups. These differences were in part due to the more immediate antipyretic effect of aspirin in comparison with ACTH and the slowly absorbed intramuscular cortisone. This is borne out by the proportions of cases febrile on the day before therapy was started in the ACTH (61.7 per cent), cortisone (58.1 per cent) and aspirin (53.0 per cent) groups.

The pulse during sleep and the erythrocyte sedimentation rates reveal no material difference (table 3). Their mean values also showed no real differences, the average pulse during sleep being 93, 93 and 90, and the average sedimentation rate 46.7, 46.2 and 45.1, for the ACTH, cortisone and aspirin groups, respectively.

Within each country, the treatment groups do not differ appreciably in their incidence of joint involvement, subcutaneous nodules and erythema marginatum, but there appears to be some difference in these respects between the two countries. The proportion of cases showing these signs (table 3) were: joint involvement U. K. 36.7 per cent, U. S. 49.4 per cent; subcutaneous nodules U. K. 21.7 per cent, U. S. 7.4 per cent; erythema marginatum U. K. 7.9 per cent, U. S. 3.9 per cent. The last difference might well be due to chance but the first two (joint involvement and subcutaneous nodules) are statistically significant ($p < 0.05$). On the other hand, subdivision of these cases into early, medium or late (tables 10 and 15) suggests that there is no real difference between the two countries in the incidence of joint involvement. Nodules were observed more frequently in the U. K. at each stage, and particularly in the late cases.

Returning to table 3, chorea was recorded more frequently in the U. K.; in both countries chance factors brought fewer cases into the ACTH group and more into the aspirin. Thus, in the total group of 162 on ACTH, 167 on cortisone and 168 on aspirin, there were 9, 19 and 26 cases with chorea as a presenting symptom. Severe cases, however, numbered only four, two and five.

For a general picture of the status of the heart at the start of therapy, the 497 cases have been divided (table 4) into groups depending on the presence or absence of pre-existing rheumatic heart disease and carditis (as defined in the diagnostic criteria). Groups A and B contain all the cases without evidence of pre-existing heart disease at the time of admission. Group A includes: (1) cases with no carditis; (2) cases with murmurs of questionable

gnificance (doubtful carditis); (3) cases with no, or oubtful, carditis but with a prolonged P-R interval. roup B includes cases with definite carditis at the tart of therapy. Within both these groups, the umber of cases with a definite previous history of heumatic fever was negligible. Group C contains all hose with definite or doubtful pre-existing rheumatic eart disease, whether or not carditis was also present. Both groups B and C are further subdivided nto (1) cases with, and (2) cases without, pericarditis nd/or failure at the start of therapy.

Table 4 shows that the cases analyzed in this way ave in general fallen equally into the three treatnent groups. The main departure lies in a somewhat ower number of cases on ACTH in group B (no re-existing heart disease, carditis present at start f treatment). In the less important C group, in which the course of the disease is difficult to analyze because of pre-existing rheumatic heart disease, here is some predominance of cases with pericarditis and/or failure in the ACTH group.

Returning to the incidence of the individual signs of involvement of the heart at start of therapy, table 3 shows, for ACTH, cortisone and aspirin, respectively, no appreciable differences for apical systolic murmurs (72.2 per cent, 70.7 per cent and 66.1 per cent), basal diastolic murmurs (25.3 per cent, 23.4 per cent and 22.0 per cent) and the proportion of cases with atrioventricular conduction time of 0.18 second or more (33.3 per cent, 34.4 per cent and 28.3 per cent). The proportion with a cardiothoracic ratio of 0.55 or more was not equal, there being a smaller proportion in the aspirin group (22.0 per cent, 18.5 per cent and 11.8 per cent), but as will be seen in the section on heart size (table 20), this is largely due to the unequal distribution of cases with pre-existing heart disease (group C). There was also a somewhat larger number of cases in failure at the start of therapy in the ACTH group, compared with the cortisone and aspirin groups (14.2 per cent, 9.0 per cent and 6.0 per cent).

Between the two countries, the individual signs of cardiac involvement were equally reported except for basal diastolic murmurs. These were more often reported in the U. K. (35.8 per cent) than in the U. S. (12.1 per cent), but this difference came from one U. K. center only. Ninety-three of the 240 U. K. cases came from this center, where the incidence of basal diastolic murmurs was 73.1 per cent. In the remainder of the U. K. centers, the incidence was 2.2 per cent.

In short, these comparisons show that in many espects the three treatment groups were very simiar, viz., in the duration-from-onset, age, sex, body veight, temperature, pulse during sleep, erythrocyte edimentation rate, frequency of polyarthritis, ubcutaneous nodules, erythema marginatum, and n the P-R interval. There are, however, a few lifferences. The group on aspirin included an undue proportion with chorea as a presenting symptom, although the few severe cases of chorea fell fairly equally in the three treatment groups. The ACTH group contained a larger proportion of cases with pericarditis and/or failure (particularly in the U. S.) and the aspirin group contained rather fewer (particularly in the U. K.). These differences are not

TABLE 4.—*Condition of the Heart at Start of Therapy, by Duration from Onset. U. K. and U. S., All Cases*

Cardiac Group and Treatment Group	Total	Duration from Onset		
		0–14 days	15–42 days	43+ days
Cardiac group A—no or questionable carditis;* no pre-existing heart disease				
ACTH	40	30	6	4
Cortisone	39	29	6	4
Aspirin	38	26	10	2
Total group A	117	85	22	10
Cardiac group B—carditis present; no pre-existing heart disease				
ACTH	74	34	29	11
Cortisone	89	38	29	22
Aspirin	89	44	24	21
Total group B	252	116	82	54
Cardiac group C—with definite or questionable pre-existing heart disease				
ACTH	48	22	12	14
Cortisone	39	18	10	11
Aspirin	41	14	12	15
Total group C	128	54	34	40
Cases with failure and/or pericarditis included in cardiac group B				
ACTH	13	4	6	3
Cortisone	14	3	7	4
Aspirin	10	7	—	3
Total	37	14	13	10
Cases with failure and/or pericarditis included in cardiac group C				
ACTH	14	5	4	5
Cortisone	10	5	3	2
Aspirin	7	3	—	4
Total	31	13	7	11

* Questionable carditis includes 8 ACTH, 6 cortisone and 7 aspirin cases with a grade P murmur and 13 ACTH, 12 cortisone and 10 aspirin cases with a prolonged P-R interval and either no murmur or grade P murmur (see *Murmur* footnote, page 360).

large but must be borne in mind in the study of the response of the illness to the different treatments.

Results

The course of rheumatic fever was followed in each case after admission to the study during the six-week period of treatment, three-week period of observation, at monthly intervals for six months following the end of the observation period and at two-month intervals until the end of the first year (quarterly thereafter). This report includes an analysis of each symptom, sign and laboratory test considered as evidence of active rheumatic fever or of rheumatic heart disease through a period of one year following the end of the observation period.

Each manifestation is considered at specified points of time and discussed individually. The methods of analysis include: comparison of averages; the proportion with a change greater than an arbitrary maximum amount; the proportion with a manifestation present or absent; the number, or percentage, above or below an arbitrary limit of normal. (With this last method of analysis, a constant number, or percentage, over a period of time does not indicate that the same cases continue abnormal but that of all the cases at risk the number abnormal remains the same.) In general, when several such indices yielded the same results, the simplest is reported; when two methods yielded differing results, both are reported. When a difference between treatment groups in one of these measurements is significant, the probability value is reported; otherwise, differences in results between treatments are not significant.

TABLE 5.—*Temperature: Percentage of Cases with a Rectal Temperature of 100.4 F or Above at Specified Times.* U. K. and U. S., All Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy 1	2	3	4	5	6	Week of Observation 7	8	9
All cases											
ACTH	162	53.7	5.8	6.0	6.6	8.9	5.8	13.4	19.3	9.7	9.6
Cortisone	167	61.1	6.8	5.2	6.8	7.0	6.4	4.8	18.2	19.1	12.2
Aspirin	168	40.5	9.7	10.3	11.3	9.1	8.9	12.8	17.0	11.9	9.5
Febrile cases at start of treatment											
ACTH	87	100.0	5.8	7.7	6.9	10.0	6.5	14.1	21.8	9.6	6.7
Cortisone	102	100.0	6.5	6.2	7.0	7.6	5.6	4.3	20.6	20.9	12.0
Aspirin	68	100.0	12.7	15.7	16.7	14.3	8.3	13.7	20.2	13.6	12.5
Afebrile cases at start of treatment											
ACTH	75	0.0	5.8	4.0	6.2	7.6	4.9	12.5	16.4	9.9	12.9
Cortisone	65	0.0	7.3	3.6	6.7	6.2	7.7	5.6	14.5	16.4	12.5
Aspirin	100	0.0	7.7	6.7	7.7	5.7	9.4	12.1	14.9	10.7	7.4

* To reduce irregularities, the values given for the end of the weeks are based upon all the observations made on *three* days centered at the end of the week, i.e. 6, 7 and 8 for week 1; 13, 14, and 15 for week 2, and so on up to days 62 and 63 for week 9.

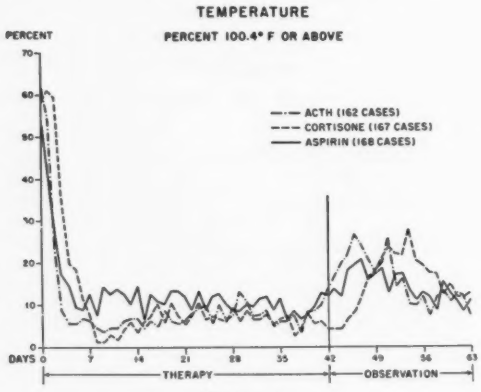

CHART 1

Temperature

Temperatures were measured four times a day throughout the nine-week period of treatment and observation. The maximum reading for each day is used in this analysis, and cases are considered febrile if that reading (rectal) was 100.4 F. or above. The three groups were comparable on the day prior to treatment (chart 1). Following start of treatment, the proportion of febrile cases decreased rapidly in all three groups, although it was most rapid on the first day in the aspirin group (table 5, chart 1). During the latter part of the first week the proportion febrile in the ACTH group was lower than that of the other two groups, but at the end of the week, all three groups were in the same range, the aspirin group lagging slightly behind. In the main this lag in the aspirin group persisted throughout the six-week period of treatment and was more prominent among the cases febrile than among those afebrile at start of treatment.

At the end of the sixth week of treatment, there was a rise in the proportion of febrile cases in the ACTH group, persisting into the eighth week and then slowly decreasing. A similar rise occurred in the cortisone group, beginning in the seventh week, reaching a peak in the eighth and decreasing slowly during the ninth week. The aspirin group showed a smaller rise with its peak in the seventh week, and decreasing during the eighth and ninth weeks. At the end of the ninth week all three groups had about the same proportion of febrile and afebrile cases (table 6).

TABLE 6.—*Temperature: Distribution at End of Ninth Week. U. K. and U. S., All Cases*

Rectal Temperature °F	Number with Given Temperature at the End of the Ninth Week		
	ACTH	Cortisone	Aspirin
97.4–	3	4	5
98.4–	33	47	41
99.4–	104	92	101
100.4–	18	18	12
101.4+	1	1	1
Not stated	3	5	8
Total	162	167	168

Pulse Rate During Sleep

The pulse rate was taken during sleep, between the hours of 12 midnight and five a.m. At start of treatment (table 7), 31 per cent to 35 per cent of the patients in each group had a pulse rate of 100 per minute or more (tachycardia) while less than 5 per cent had a rate of less than 60 per minute (bradycardia).

Following start of treatment there was a slight rise in the proportion with tachycardia among the cortisone cases during the first two days (chart 2). Apart from this, the proportion decreased at approximately the same rate in all three groups, reaching the same level in cortisone and aspirin at the end of the first week, the ACTH group having a slightly higher figure. These relative proportions remained unchanged throughout the treatment period. When therapy was stopped, there was a sharp rise in the ACTH group and a slower rise to the same level in the cortisone group. At the end of the observation period, one-fifth

TABLE 7.—*Pulse Rate During Sleep: Percentage of Cases with Bradycardia (Under 60) and Tachycardia (100 and Over) at Specified Times.* U. K. and U. S., All Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy						Week of Observation		
			1	2	3	4	5	6	7	8	9
Percentage with bradycardia											
ACTH	162	4.6	14.7	10.9	7.4	6.1	3.8	2.5	0.0	0.6	0.7
Cortisone	167	2.0	18.3	24.7	13.7	12.0	8.3	6.9	2.0	0.4	0.3
Aspirin	168	4.1	4.8	10.0	9.3	7.1	4.3	1.6	3.8	1.5	4.3
Percentage with tachycardia											
ACTH	162	35.8	13.9	10.7	9.6	13.9	12.7	13.3	24.6	21.4	21.3
Cortisone	167	34.6	10.1	6.5	7.2	7.5	6.3	5.9	13.2	22.7	20.1
Aspirin	168	30.6	10.1	7.9	6.9	7.3	5.3	6.8	10.7	8.8	6.7

* See footnote, table 5.

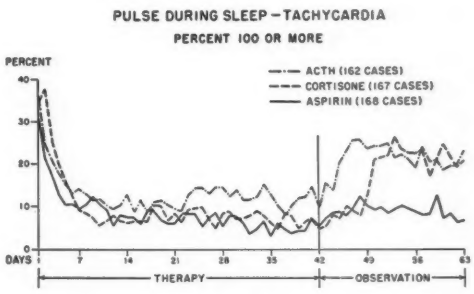

CHART 2

of the cases in both groups still had tachycardia. On the other hand, the proportion with tachycardia in the aspirin group remained almost unchanged when treatment ended and throughout the observation period.

Detailed analysis showed that in all treatment groups there was the same rapid fall in the proportion with tachycardia among the cases of short duration (0 to 14 days) while in those of longer duration (15 plus days) it fell more slowly. Thus starting from the same level of 30 per cent to 40 per cent with tachycardia, there was a fall at the end of the first week to only 1 per cent to 8 per cent among the cases of short duration in comparison with 13 per cent to 22 per cent among those of longer duration. This latter group lagged behind until the fourth or fifth week.

The proportion with bradycardia increased sharply after the start of treatment in both

TABLE 8.—*Erythrocyte Sedimentation Rate: Percentage of Cases with a Rate of 20 mm in 1 hour, or Higher (Uncorrected) at Specified Times.* U. K. and U. S., All Cases*

Treatment Group	No. of Cases	Start of Therapy	Week of Therapy						Week of Observation			Follow-up	
			1	2	3	4	5	6	7	8	9	13 wks.	1 year
ACTH	162	91.9	64.3	28.1	17.1	20.3	22.8	20.6	47.2	43.0	32.2	11.6	10.3
Cortisone	167	90.0	87.3	46.1	38.8	28.2	23.0	19.1	24.8	44.1	41.8	16.1	12.8
Aspirin	168	91.5	79.0	66.7	49.4	39.6	32.9	22.0	24.8	23.6	21.8	13.5	12.8

* The observations were not always made on the final day of the week, but were, in most cases, made at weekly intervals. A margin of ±3 days was allowed in deriving weekly values.

hormone groups, reaching 14.7 per cent in the ACTH group at the end of the first week and almost 25 per cent in the cortisone group at the end of the second week (chart 3). From this point, the proportion with bradycardia decreased to approximately the starting level by the end of the treatment period. In contrast, bradycardia occurred later in the aspirin group reaching a peak of a little over 10 per cent in the second to third weeks and declining thereafter.

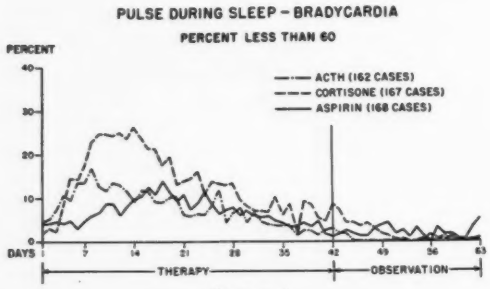

CHART 3

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate was measured by the Wintrobe method[6] (uncorrected)* at the start of treatment, weekly

* A corrected sedimentation rate of 15 mm. in 1 hour or above was established as a minor diagnostic criterion for admission to the study and was so used. In analyzing the course of the disease for the first 13 weeks, an uncorrected rate of 20 mm. in 1 hour or above was used, because (1) the centrifuges used in the hematocrit determinations were not standardized, with resulting variation from center to center, and (2) analysis of uncorrected and corrected readings for each of the drugs showed the same trends and it seemed undesirable to introduce an unnecessary variable.

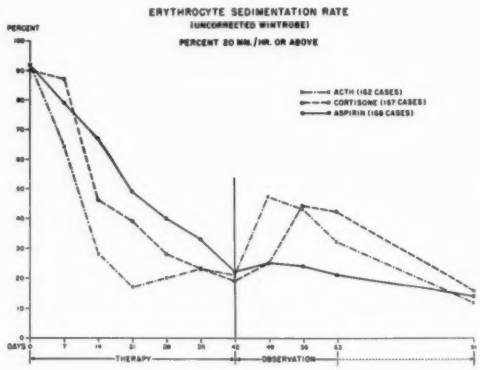

CHART 4

throughout the treatment and observation period, and at each follow-up examination. Its course was followed by tabulation of the proportion of cases with a rate of 20 mm. in 1 hour or above at specified times.

At the start of treatment, approximately 90 per cent of the cases in each treatment group had an elevated sedimentation rate. This proportion decreased rapidly in the hormone groups, with the ACTH group showing the sharpest drop, levelling off at the third week, in contrast to the cortisone group which reached roughly this same level about the fifth week (table 8, chart 4). The proportion of those with an elevated rate in the aspirin group lagged distinctly behind that of both hormone groups, not reaching the same level until the last week of treatment. When treatment was stopped, however, there was a sharp rise in the proportion with a raised rate in the ACTH group and a slower rise to the same level in the cortisone group while there was no change in the aspirin group. By the thirteenth week, the proportion in all three groups had reached the

ame low level of 12 to 16 per cent. The very milar distribution of values at this point is hown in table 9; at one year the proportions ere relatively unchanged from the 13-week gures. Separate analysis showed that these rends were the same for all three duration-rom-onset groups.

To summarize, during treatment the pro-ortion with an elevated sedimentation rate ecreased much more rapidly in the hormone roups than in the aspirin group, but it in-reased sharply though temporarily in both hormone groups after treatment was stopped in contrast to a negligible change in the aspirin group. It finally reached the same low level in all three groups at 13 weeks and this equal level was maintained at one year.

*Joint Involvement**

At start of therapy there was a greater proportion of cases with joint involvement in the U. S. centers (49.4 per cent) than in the U. K. (36.7 per cent), the difference occurring entirely among the early cases (table 10). In both countries, the percentages were about the same in each treatment group.

In each treatment group, cases with joint involvement on admission rapidly lost this symptom. Thus, on the third day of therapy, joint involvement was still present in 28.6 per cent of ACTH, 56.4 per cent of cortisone and 36.5 per cent of aspirin cases. By the eighth day, it remained in less than 10 per cent in each treatment group. Throughout the rest of the treatment period, joint involvement was present in none of the cortisone cases, in only a rare case in the ACTH group and in a few cases in the aspirin group (table 11). After treatment was stopped, there was an insignificant increase of cases with joint involvement in the ACTH group, and these had

* Polyarthritis as a major manifestation for diagnosis of rheumatic fever was defined as "pain and either limitation of active motion, or tenderness in two or more joints." For following the course of this manifestation after start of treatment, a system of grading was adopted in which the lowest grade was defined as joint pain without objective joint findings. Since this lowest grade is less than that required for the definition of polyarthritis, the course of the manifestation is referred to as "joint involvement".

TABLE 9.—*Erythrocyte Sedimentation Rate: Distribution at 13 Weeks. U. K. and U. S., All Cases*

Erythrocyte Sedimentation Rate (mm in 1 hr. uncorrected)	Number with Given Rate at 13 Weeks		
	ACTH	Cortisone	Aspirin
0–19	137	130	134
20–29	13	20	14
30–39	2	4	3
40–49	3	1	2
50–59	—	—	2
Not stated	7	12	13
Total	162	167	168

TABLE 10.—*Joint Involvement: Comparison of U. K. and U. S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in days)	U. K.			U. S.		
	Total cases	With joint involvement		Total cases	With joint involvement	
		Number	Per cent		Number	Per cent
0–14	109	57	52.3	146	101	69.2
15–42	79	20	25.3	59	13	22.0
43+	52	11	21.2	52	13	25.0
Total	240	88	36.7	257	127	49.4

TABLE 11.—*Cases with Joint Involvement at Start of Therapy: Number and Per cent with Joint Involvement at Specified Times. U. K. and U. S., All Cases*

Time from Start of Therapy	ACTH		Cortisone		Aspirin	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
1 day	63	100.0	78	100.0	74	100.0
2 days	41	65.1	59	75.6	52	70.3
3	18	28.6	44	56.4	27	36.5
4	12	19.0	27	34.6	11	14.9
5	5	7.9	17	21.8	9	12.2
6	7	11.1	13	16.7	9	12.2
7	5	7.9	8	10.3	9	12.2
8	4	6.3	6	7.7	6	8.1
15	1	1.6	—	0.0	6	8.1
22	2	3.2	—	0.0	5	6.8
29	1	1.6	—	0.0	6	8.1
36	2	3.2	—	0.0	2	2.7
43	2	3.2	—	0.0	4	5.4
50	3	4.8	8	10.3	6	8.1
57	2	3.2	7	9.0	5	6.8
63	1	1.6	—	0.0	2	2.7
13 weeks	—	0.0	1	1.3	2	2.7

TABLE 12.—*Cases Without Joint Involvement at Start of Therapy: Development of Joint Involvement During Specified Intervals. U. K. and U. S., All Cases*

Treatment Group	Number of Cases Without Joint Involvement at Start of Therapy	Number Developing Joint Involvement		
		1–42 days	43–63 days	at 13 weeks
ACTH	99	4	5	—
Cortisone	89	5	4	—
Aspirin	94	—	4	—

TABLE 13.—*Cases with Chorea at Start of Therapy: Subsequent Course. U. K. and U. S., All Cases*

Treatment Group	Number of Cases with Chorea at Start of Therapy	Number with Chorea at		
		End of therapy week 6	End of observation week 9	Follow-up 13 weeks
ACTH	9	1	—	1
Cortisone	19	2	1	3
Aspirin	26	9	5	9

TABLE 14.—*Cases Without Chorea at Start of Therapy: Development of Chorea During Specified Time Intervals. U. K. and U. S., All Cases*

Treatment Group	Number of Cases Without Chorea at Start of Therapy	Number Developing Chorea		
		1–42 days	43–63 days	at 13 weeks
ACTH	153	3	—	—
Cortisone	148	3	—	2
Aspirin	142	4	—	1

TABLE 15.—*Nodules: Comparison of U. K. and U. S. Cases at Start of Therapy*

Duration from Onset at Start of Therapy (in Days)	U. K.			U. S.		
	Total cases	With nodules		Total cases	With nodules	
		Number	Per cent		Number	Per cent
0–14	109	6	5.5	146	2	1.4
15–42	79	14	17.7	59	7	11.9
43+	52	32	61.5	52	10	19.2
Total	240	52	21.7	257	19	7.4

disappeared by the 13th week; in the cortisone group there was an immediate rise to 10.3 per cent followed by complete disappearance at the ninth week and one recurrence at the thirteenth week; in the aspirin group two cases continued up to the thirteenth week. Among cases in which joint involvement disappeared, it later reappeared in only a few cases (ACTH 5, cortisone 15 and aspirin 8).

Among cases *without* joint involvement at start of therapy (table 12), a few developed it during the 13-week period (ACTH 9, cortisone 9, aspirin 4). In five ACTH, four cortisone and in the four aspirin cases, the joint involvement appeared for the first time after the end of treatment.

There is little to choose among the three drugs in their effect on joint involvement apart from some delay in response to cortisone administered intramuscularly.

Chorea

At the start of therapy, there was a larger proportion of cases with chorea in the aspirin group than in either of the hormone groups. Chorea seemed to persist longer in the aspirin than in the hormone groups, but this difference is not significant (table 13). The persistence of this symptom was strikingly more pronounced in the U. K. than in the U. S. cases, since at 13 weeks nearly all were in U. K. centers (the ACTH case, one of three cortisone and eight of nine aspirin cases).

Among the cases *without* chorea at the start of therapy, a few in all three treatment groups developed this symptom at some time during the 13-week period (table 14).

The persistence of chorea, as well as its appearance for the first time, was not significantly different between the treatment groups.

Subcutaneous Nodules

At start of therapy, there was a significantly larger proportion of cases with subcutaneous nodules in the U. K. (21.7 per cent) than in the U. S. (7.4 per cent), most of the difference occurring in the group of late cases (table 15). Among the three treatment groups in the two countries, however, such cases were fairly evenly distributed except for slightly fewer in the aspirin group.

In most of the early and medium duration cases (0 to 42 days) receiving ACTH or cortisone, subcutaneous nodules had disappeared by the end of treatment (table 16). In the

TABLE 16.—*Cases with Nodules at Start of Therapy: Subsequent Course. U. K. and U. S., All Cases*

Treatment Group and Duration from Onset	Number with Nodules at Start of Therapy	Number with Nodules Persisting to		
		End of therapy week 6	End of observation week 9	Follow-up 13 weeks
1–42 days				
ACTH	13	4	1	—
Cortisone	12	4	2	1
Aspirin	4	3	2	1
43 days +				
ACTH	13	6	4	3
Cortisone	13	7	4	1
Aspirin	16	12	12	10
		Number in Which *Fresh* Nodules Appeared		
		1–42 days	43–63 days	at 13th week
All duration groups				
ACTH	26	5	2	1
Cortisone	25	3	—	—
Aspirin	20	9	2	1

aspirin group, although the number with nodules was fairly small, the nodules tended to persist to the end of the sixth week. This tendency was even more apparent among the chronic cases (43 plus days) although the rate of disappearance in these cases was perhaps lower with all three drugs. These differences in response came from the U. K. cases, since at the end of six weeks, only two, and at 13 weeks, only one with nodules still remaining were U. S. cases.

New subcutaneous nodules developed in some cases during the treatment period in all treatment groups, and particularly among cases with nodules at the start of therapy (tables 16 and 17). During the treatment period, there was a slightly greater tendency for cases in the aspirin group to develop new nodules than among those in the hormone groups. Of the 36 cases, in 11 treatment groups, in which new nodules developed during therapy, 25 were U. K. cases.

Thus, it may be concluded that new nodules appeared on all treatments and that nodules persisted longer in the aspirin than ACTH and cortisone treated cases.

TABLE 17.—*Cases Without Nodules at Start of Therapy: Development of Nodules During Specified Time Intervals. U. K. and U. S., All Cases*

Treatment Group	Number of Cases Without Nodules at Start of Therapy	Number Developing Nodules		
		1–42 days	43–63 days	at 13 weeks
ACTH	136	7	—	1
Cortisone	142	2	—	—
Aspirin	148	10	1	1

TABLE 18.—*Cases with Erythema Marginatum at Start of Therapy: New Episodes of Erythema Marginatum. U. K. and U. S., All Cases*

Treatment Group	Number of Cases with Erythema Marginatum at Start of Therapy	New Episodes Developing		
		1–42 days	43–63 days	at 13 weeks
ACTH	12	5	1	—
Cortisone	11	2	2	—
Aspirin	6	2	1	—

TABLE 19.—*Cases Without Erythema Marginatum at Start of Therapy: Development of Erythema Marginatum During Specified Time Intervals. U. K. and U. S., All Cases*

Treatment Group	Number of Cases Without Erythema Marginatum at Start of Therapy	Number Developing Erythema Marginatum		
		1–42 days	43–63 days	at 13 weeks
ACTH	150	9	1	—
Cortisone	156	10	5	—
Aspirin	162	9	1	1

Erythema Marginatum

At the start of therapy, there were 29 cases with erythema marginatum (ACTH 12, cortisone 11, aspirin 6). The proportion with new episodes developing during treatment and observation was similar for all treatment groups (table 18). At 13 weeks, erythema marginatum had persisted in two ACTH cases and one aspirin case.

Among the cases *without* erythema marginatum at start of treatment, the number developing episodes for the first time during treatment or observation was also similar for all treatment groups (ACTH 10, cortisone 15 and aspirin 11) (table 19). Among these cases only one remained at 13 weeks, a cortisone case

TABLE 20.—*Cardiothoracic Ratio: Percentage of Cases in Cardiac Groups with TD/ID Ratio of 0.55 or More at Specified Times,* U. K. and U. S., All Cases*

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac group A—no or questionable carditis, no pre-existing heart disease						
ACTH	40	2.6	0.0	0.0	2.7	2.9
Cortisone	39	2.7	2.9	0.0	0.0	0.0
Aspirin	38	0.0	0.0	0.0	0.0	0.0
Cardiac group B†—carditis present, no pre-existing heart disease						
ACTH	61	5.0	8.3	12.1	8.6	10.2
Cortisone	75	10.7	7.1	10.3	8.4	6.0
Aspirin	79	9.2	13.9	6.4	7.8	5.8
Cardiac group C†—with definite or questionable pre-existing heart disease						
ACTH	34	27.3	30.3	28.1	29.0	13.8
Cortisone	29	29.6	28.6	31.0	37.0	17.4
Aspirin	34	15.2	15.2	15.2	9.4	16.0
Congestive failure and/or pericarditis						
ACTH	27	81.5	66.7	68.0	64.0	47.8
Cortisone	24	56.5	50.0	52.2	31.8	19.0
Aspirin	17	43.8	58.8	41.2	31.2	27.3
All groups						
ACTH	162	22.0	20.8	21.6	20.5	15.6
Cortisone	167	18.5	16.1	17.9	14.8	8.5
Aspirin	168	11.8	15.7	10.2	8.9	8.0

* At the specified times, there were sometimes a few observations missing. Percentages are based on the number available.

† Excluding cases with failure and/or pericarditis at start of therapy.

which first manifested erythema marginatum during the observation period. In addition, there was one aspirin case in which erythema marginatum appeared for the first time at the thirteenth week.

Thus the rate of appearance or disappearance of episodes of erythema marginatum appeared unrelated to therapy.

Heart Size

Variations in heart size were analyzed by three methods:

1.—The proportion in each treatment group with a cardiothoracic ratio of 0.55 or more; this method described extreme grades of cardiac enlargement.

2.—The frequency of change in transverse cardiac diameter of 0.6 cm. or more, between 0 and 3, 3 and 6, and 6 and 9 weeks and 0 and 1 year; this method, although starting from an abnormal baseline, was more sensitive than method to temporary changes of a lesser degree.

3.—The proportion of cases with a cardiothoracic ratio of 0.50 or more; this method yielded no additional information and will not be further discussed.

In cardiac group A, the proportion with a cardiothoracic ratio of 0.55 or more in any treatment group at any time was insignificant (table 20). In cardiac group B (excluding those with failure or pericarditis or both), the approximately equal distribution among the three treatment groups persists throughout. In cardiac group C (excluding those with failure or pericarditis or both), there was a smaller proportion of cases initially in the aspirin group with extreme grades of cardiac enlargement. This inequality persists at three, six and nine weeks but disappears at one year. In the group of cases with failure or pericarditis or both, the relative inequality persists throughout.

Using the more sensitive index of change in heart size of 0.6 cm. or more, a larger proportion showed an increase over the 0 to 9 week period in each hormone compared with the aspirin group. This difference appeared early, since analysis of the 0 to 3- and 3 to 6-week intervals showed the same result, but at one year it had disappeared (chart 5). In contrast, the proportion showing a decrease in heart size was similar for all treatment groups. Cardiac groups A, B and C all showed this difference between each of the hormones and aspirin early in treatment and the same equality at the end of one year. Among cases with failure and/or pericarditis (in which the proportion of enlarged hearts was high at start of therapy), approximately one third showed an early decrease regardless of therapy and few (16 per cent) showed an increase during treatment.

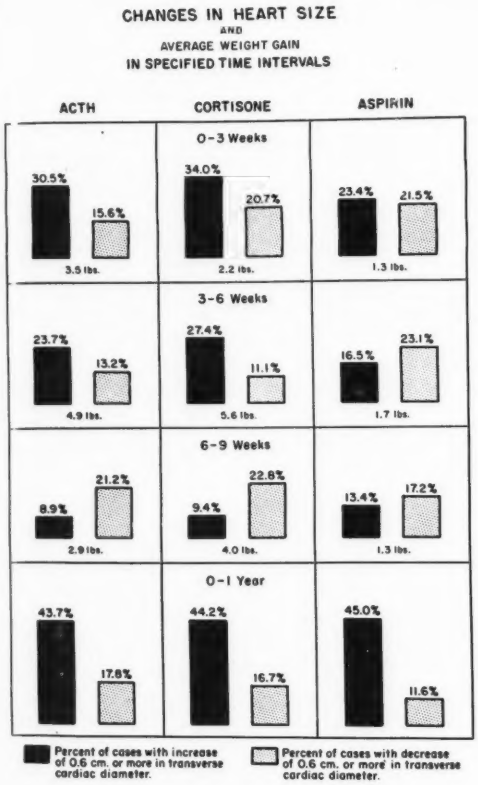

CHART 5

Considering gains in body weight, increases in heart size were more frequent in each hormone group than in the aspirin group during 0 to 3 and 3 to 6 weeks, but not during 6 to 9 weeks. In each period, however, both hormone groups had an average weight gain two to three times as great as the aspirin group; in other words, there was no clear relationship between weight gain and increase in heart size.

In summary, when heart size is measured by the proportion with a cardiothoracic ratio of 0.55 or more, the cardiac subgroups and the total cases reveal no differences between treatments. Using the more sensitive index of change in heart size of 0.6 cm. or more, there is a tendency for cases treated with ACTH or cortisone to show a temporary increase in heart size.

Atrioventricular Conduction Time

The course of the atrioventricular conduction time* (measured by the P-R interval in the electrocardiogram) was analyzed using:

1.—The percentage with a P-R interval of 0.18 second or longer.
2.—The percentage with a P-R interval of 0.16 second or longer.
3.—The average P-R interval.
4.—The percentage with an increase or decrease in the P-R interval of 0.03 second or more during the interval of 0 to 3, 0 to 6, 6 to 9 and 0 to 9 weeks.

The four methods led to the same conclusions and only the percentages with a P-R interval of 0.18 second or longer are presented here.

The proportions of cases with a P-R interval of 0.18 second or longer are distributed fairly equally at start of therapy in each of the treatment and each of the cardiac groups (table 21, chart 6). They decreased initially more rapidly among those receiving ACTH or cortisone than among those receiving aspirin, with the ACTH group showing a very rapid fall at the end of the first week from 33.3 per cent to 8.7 per cent and in the second week to 6.9 per cent. At the third week, the ACTH and cortisone groups were at the same level, with the aspirin group clearly lagging behind. This difference was maintained to the end of the treatment period after which, at nine weeks and at one year, all three groups were in the same range (13 per cent to 19 per cent). This decrease during treatment in the hormone treated cases occurred in all cardiac groups but was less marked in cardiac group C.

The hormones appear to decrease the P-R interval to values below those at nine weeks and at one year. The values at these later times

* The diagnostic criteria for admission of patients to the study defined normal P-R intervals as corrected for age and heart rate according to the Ashman-Hull[4] tables. These corrections were not used in evaluating the course of the disease because the P-R intervals were unduly influenced by marked pulse rate changes, and because recent unpublished studies of the P-R interval in normal children by the Child Research Council of Denver question the corrections proposed by Ashman and Hull.

TABLE 21.—*Atrioventricular Conduction Time: Percentage of Cases in Cardiac Groups with P-R Interval of 0.18 Sec. or Above at Specified Times.* U. K. and U. S., All Cases*

Cardiac Group and Treatment Group	No. of Cases	Start of Therapy	Week 3	End of Therapy Week 6	End of Observation Week 9	Follow-up One Year
Cardiac group A—no or questionable carditis, no pre-existing heart disease						
ACTH	40	36.8	5.3	5.7	7.1	6.5
Cortisone	39	40.5	8.1	11.1	13.6	18.5
Aspirin	38	30.6	13.3	15.2	20.0	0.0
Cardiac group B†—carditis present, no pre-existing heart disease						
ACTH	74	28.2	6.1	6.0	14.3	14.3
Cortisone	89	29.3	7.3	11.4	12.7	22.5
Aspirin	89	25.6	14.5	13.8	10.0	12.3
Cardiac group C†—with definite or questionable pre-existing heart disease						
ACTH	48	38.3	20.5	15.9	25.6	30.8
Cortisone	39	40.0	13.9	10.8	24.2	11.1
Aspirin	41	32.4	28.2	27.5	20.0	25.9
All groups						
ACTH	162	33.3	10.1	8.9	16.4	17.5
Cortisone	167	34.4	9.0	11.2	15.9	19.2
Aspirin	168	28.3	17.8	17.6	14.4	12.5

* See first footnote, table 20.

† Includes cases with failure and/or pericarditis at start of therapy.

might well be expected to be closer to normal than those recorded during the acute illness. It may be questioned, therefore, whether the early decrease in P-R intervals is an effect of the hormones on the disease or merely a direct effect on the atrioventricular conduction time.

Murmurs

*Apical Systolic and Basal Diastolic Murmurs.** The development and course of significant heart murmurs are among the most important aspects of rheumatic fever. They are analyzed during the acute attack (0 to 13 weeks) and at one year, according to the status of the heart at the start of treatment, i.e. group A, those without pre-existing heart disease or carditis; group B, those with carditis and without pre-existing heart disease; and group C, those with pre-existing heart disease.

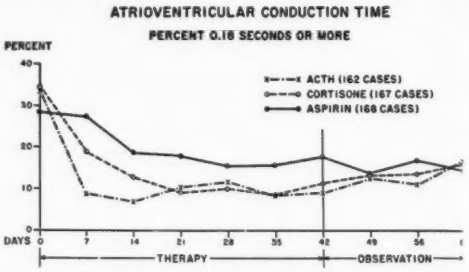

CHART 6

Cardiac Group A: Each treatment group included approximately the same number of cases without carditis or pre-existing heart disease. None of these had an apical systolic or basal diastolic murmur on admission to the study. During the nine-week period of treatment and observation, it was unusual for either of these murmurs to appear, and at 13 weeks, few cases had either an apical systolic or a basal diastolic murmur or both, regardless of the type of therapy (table 22). At 13 weeks, among 40 ACTH cases there were five with apical systolic murmurs; among 39 cortisone cases, there was one with an apical systolic murmur, one with a basal diastolic murmur and one with both; and among the 38 aspirin cases there were two with apical systolic murmurs. At one year apical systolic murmurs were still few: five in the ACTH group, four in the cortisone and five in the aspirin group. One of the cortisone cases also had a basal diastolic murmur. In other words, if a case of rheumatic fever meeting the criteria for admission to this study had no apical systolic or basal diastolic murmur at the time, the chance of developing, either during the acute

* In this study, the following grades were adopted for reporting apical systolic murmurs:

Grade 0—No murmur, or a murmur considered to be "functional" on the basis of its apparent origin at the pulmonic area or along the left sternal border.

Grade P—Murmur apparently localized to the apical area, but so faint as not to be transmitted to or toward the axilla.

Grade 1—Soft apical systolic murmur transmitted to or toward the axilla.

Grade 2—Louder similar murmur.

Grade 3—Very loud similar murmur, usually transmitted to the back.

In the analysis of the data, the "P" murmurs were included under grade 0.

attack or at one year, was only approximately 1 in 8, regardless of treatment.

Cardiac Group B: Among the cases with carditis without pre-existing heart disease, the distribution of apical systolic murmurs by grades was not the same in the three treatment groups at start of therapy; there were relatively more grade 0 and grade 2 murmurs among the aspirin, grade 1 among the cortisone and grade 3 among the ACTH cases. For this reason, analysis of the group as a whole becomes complicated and each grade is analyzed separately.

TABLE 22.—*Cardiac GroupA (No Carditis, No Pre-Existing Heart Disease): Murmurs Present at Specified Times. U. K. and U. S., All Cases*

	Total Cases	Number with Murmurs at			
		End of therapy week 6	End of observation week 9	Follow-up 13 weeks	Follow-up one year
ACTH	40	3	5	5	5
Cortisone	39	2	1	3	4
Aspirin	38	3	2	2	5

The group B cases without an apical systolic murmur at start of therapy (included in group B on account of other murmurs, increase in heart size, failure or pericarditis) behaved much like the cases without carditis (group A); it was unusual for them to develop an apical systolic murmur during the first 13 weeks following the start of treatment or at one year regardless of the treatment employed (table 23).

In group B cases, grade 1 apical systolic murmurs at the start of treatment appeared to respond differently during the acute attack in hormone-treated cases compared with the aspirin-treated cases. In the majority of the cases treated with ACTH or cortisone the grade 1 murmur disappeared by the end of six weeks of treatment. There was a slight increase in their frequency among the cortisone cases at nine weeks, but otherwise there was no appreciable change at the ninth and thirteenth weeks. By contrast, in only 4 of 18 aspirin cases did the grade 1 apical systolic murmur disappear at six weeks and in only seven by the thirteenth

TABLE 23.—*Cardiac Group B* (with Carditis, No Pre-Existing Heart Disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U. K. and U. S., All Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at End of Therapy Week 6				Grade at End of Observation Week 9				Grade at Follow-up 13 Weeks					Grade at Follow-up 1 Year				
		0	1	2	3	0	1	2	3	0	1	2	3	Not known	0	1	2	3	Not known
Grade 0																			
ACTH	5	4	—	1	—	4	—	1	—	4	—	1	—	—	5	—	—	—	—
Cortisone	8	8	—	—	—	8	—	—	—	7	—	—	—	1	7	—	—	—	1
Aspirin	12	10	2	—	—	11	1	—	—	11	—	—	—	1	11	—	—	—	1
Grade 1																			
ACTH	14	10	2	1	1	11	2	—	1	11	2	1	—	—	12	1	1	—	—
Cortisone	27	19	7	1	—	14	11	1	1	20	5	—	2	—	17	7	3	—	—
Aspirin	18	4	10	4	—	6	8	4	—	7	7	3	—	1	10	5	3	—	—
Grade 2																			
ACTH	35	9	9	15	2	7	11	15	2	6	11	14	3	1	10	9	10	3	3†
Cortisone	36	8	14	14	—	11	12	13	—	12	13	10	1	—	19	7	7	2	1
Aspirin	49	5	17	24	3	12	13	19	5	10	14	18	5	2	24	9	9	6	1†
Grade 3																			
ACTH	20	1	3	9	7	1	2	8	9	3	1	8	8	—	4	3	6	7	—
Cortisone	16	1	—	6	9	—	1	6	9	—	3	3	9	1	2	2	2	9	1
Aspirin	10	—	2	3	5	1	1	4	4	1	2	4	3	—	2	1	5	1	1
Grade not stated																			
Cortisone	2	1	—	—	1	1	—	1	—	1	—	1	—	—	1	—	—	1	—

* Includes cases with failure and/or pericarditis at start of therapy.

† Includes one death.

TABLE 24.—*Cardiac Group B* (with Carditis, No Pre-Existing Heart Disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U. K. and U. S. Cases†*

Status at Start of Therapy and Treatment Groups	Total Cases	End of Therapy Week 6		End of Observation Week 9		Follow-up 13 Weeks			Follow-up 1 Year		
		Absent	Present	Absent	Present	Absent	Present	Not known	Absent	Present	Not known
No murmur at start											
ACTH	51	48	3	49	2	48	2	1	48	1	2‡
Cortisone	62	60	2	60	2	59	2	1	58	3	1
Aspirin	68	63	5	64	4	63	2	3	62	4	2‡
Murmur present at start											
ACTH	7	1	6	1	6	2	5	—	1	5	1
Cortisone	8	3	5	3	5	5	3	—	2	5	1
Aspirin	5	2	3	2	3	2	3	—	2	3	—

* Includes cases with failure and/or pericarditis at start of therapy.

† Includes 201 cases in 11 of the 12 centers where basal diastolic murmurs were present at start of therapy in 10 per cent of cases, and excludes 51 cases in one center where basal diastolic murmurs were present in 41 cases, i.e. 80 per cent, absent in 8, undetermined in 2 because of a loud pericardial friction rub.

‡ Includes one death.

week. There were relatively few grade 1 murmurs that increased to grade 2 or 3 during the 13-week period in any of the treatment groups. At one year following the end of the observation period, the differences between the three treatment groups were no longer significant (table 23).

Grade 2 apical systolic murmurs in cases with carditis (group B) presented a somewhat different pattern. These murmurs disappeared in slightly more cortisone than ACTH or aspirin cases. Thus, by the end of 13 weeks, these murmurs had disappeared in about one-sixth of the ACTH, one-fifth of the aspirin and one-third of the cortisone cases. Considering murmurs which decreased as well as those which disappeared, the differences among the treatment groups are not so great. At the end of 13 weeks in one-half of the ACTH and aspirin cases, the grade 2 murmur had diminished or had disappeared, in comparison with five-sevenths of the cortisone cases. With the number of cases studied, none of these differences reached the 5 per cent level of significance. By the end of one year, only minor differences remained. Thus, in the group B cases, there were no striking differences in the effect of ACTH, cortisone or aspirin on grade 2 apical systolic murmurs during the acute attack or at one year.

Grade 3 apical systolic murmurs in cases with carditis did not disappear, except in a few instances, during the 13-week period or at one year, regardless of the type of treatment (table 23). Some of these loud murmurs became less intense, particularly in the aspirin group, but this difference again was not significant.

Summarizing, the apical systolic murmurs in group B cases responded in relatively the same way to the three forms of treatment, except when the apical systolic murmur was of minimum intensity (grade 1). In these cases a larger proportion of such murmurs disappeared during therapy with ACTH and cortisone than with aspirin, but there was little difference between treatment groups at the end of one year.

In 11 centers, basal diastolic murmurs in cardiac group B cases were recorded in 20 of 201 (10 per cent) while in one U. K. center they were present in 41 cases (80 per cent), absent in 8 and undetermined in 2. Two separate analyses are therefore presented.

In the 11 centers, basal diastolic murmurs were present at the start of therapy in seven of 58 ACTH, eight of 70 cortisone and five of 73 aspirin cases (table 24). At 6, 9, 13 weeks and at 1 year, the disappearance of these murmurs or their appearance in cases originally without them was approximately the same for all treatment groups.

In the one U. K. center, of eight cases initially without basal diastolic murmurs one developed a transient murmur. In 41 cases where the murmur was initially present, it had disappeared by nine weeks more frequently from the ACTH (14 of 15) than from the cortisone (6 of 13) and aspirin groups (4 of 13). The difference was still present at one year (13 of 15 ACTH, 4 of 12 cortisone and 5 of 12 aspirin).

Cardiac Group C: These cases with pre-existing heart disease, including those with additional pericarditis or failure or both on admission, are difficult to evaluate.

The disappearance of apical systolic mur-

TABLE 25.—*Cardiac Group C* (with Definite or Questionable Pre-Existing Heart Disease): Apical Systolic Murmurs, Grades at Start of Therapy and at Specified Times. U. K. and U. S., All Cases*

Grade at Start of Therapy and Treatment Group	Total Cases	Grade at End of Therapy Week 6				Grade at End of Observation Week 9				Grade at Follow-up 13 Weeks					Grade at Follow-up One Year				
		0	1	2	3	0	1	2	3	0	1	2	3	Not known	0	1	2	3	Not known
Grade 0 at start																			
ACTH	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cortisone	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Aspirin	7	5	1	1	—	4	2	1	—	4	1	—	—	2	6	1	—	—	—
Grades 1 & 2 at start																			
ACTH	32	5	8	16	3	7	6	15	4	8	3	15	5	1	7	9	12	4	—
Cortisone	23	4	8	11	—	5	8	10	—	8	5	10	—	—	6	7	9	1	—
Aspirin	23	1	2	19	1	2	5	15	1	2	3	15	3	—	6	3	13	—	1†
Grade 3 at start																			
ACTH	16	—	—	2	14	—	—	3	13	—	1	2	13	—	1	—	3	11	1
Cortisone	16	1	—	5	10	—	1	4	11	—	1	4	10	1†	1	—	5	8	2†
Aspirin	11	—	—	4	7	—	—	5	6	—	—	5	6	—	—	1	5	4	1†

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes one death.

TABLE 26.—*Cardiac Group C* (with Definite or Questionable Pre-Existing Heart Disease): Basal Diastolic Murmurs at Start of Therapy and at Specified Times. U. K. and U. S. Cases*†

Status at Start of Therapy and Treatment Group	Total Cases	End of Therapy Week 6		End of Observation Week 9		Follow-up 13 Weeks			Follow-up One Year		
		Absent	Present	Absent	Present	Absent	Present	Not known	Absent	Present	Not known
No murmur at start											
ACTH	29	26	3	27	2	26	3	—	24	5	—
Cortisone	20	18	2	18	2	18	2	—	18	2	—
Aspirin	21	20	1	19	2	17	2	2	16	3	2‡
Murmur present at start											
ACTH	9	1	8	3	6	2	7	—	2	6	1
Cortisone	12	1	11	1	11	—	11	1‡	1	10	1‡
Aspirin	8	1	7	1	7	1	7	—	2	6	—

* Includes cases with failure and/or pericarditis at start of therapy.
† Includes 99 cases in 11 of the 12 centers where basal diastolic murmurs were present at start of therapy in 29 per cent of cases, and excludes 29 cases in one center where basal diastolic murmurs were present in 93 per cent of cases.
‡ Includes one death.

murs, grades 1 and 2, during the acute attack was slower in the aspirin group; in 8 of 32 ACTH and 8 of 23 cortisone cases these murmurs had disappeared at the end of 13 weeks, as compared with 2 of 23 cases in the aspirin group (table 25). However, at one year there was very little difference between the three treatment groups. None of the 43 grade 3 apical systolic murmurs had disappeared at 13 weeks after start of therapy and only two (1 ACTH and one cortisone) had disappeared by the end of one year.

In the group C cases from 11 centers, the appearance or disappearance of basal diastolic murmurs showed no differences among the treatment groups during the acute attack or at one year (table 26). A few new basal diastolic murmurs appeared, and an insignificant number of those present disappeared during the 13 week period or at one year. In the one U. K. center, separately considered, there were also no differences between treatment groups. Only two of 29 group C cases had no basal diastolic murmurs initially and none appeared later. Where the murmur was present initially, it persisted to one year in 7 of 10 ACTH, 6 of 6 cortisone and 9 of 11 aspirin cases.

This analysis of apical systolic and basal diastolic murmurs among group C cases showed only one difference, a more rapid disappearance of lower grades of apical systolic murmurs in cases receiving ACTH and cortisone.

Apical Diastolic Murmurs. Mid-diastolic Murmurs: This analysis of mid-diastolic murmurs is limited to the data for the U. K. centers, differing from the pattern of presentation elsewhere in this report. The U. S. data are not included since a review of the records indicated that varying terms, viz., mid-diastolic murmur, third heart sound and gallop rhythm, were recorded inconsistently from center to center and from observer to observer of the same case in the same center. Further, in acute rheumatic carditis, this murmur is rarely heard in the absence of an organic apical systolic murmur which was consistently recorded. The U. S. investigators, therefore, agreed that the mid-diastolic murmur in the U. S. cases should not be analyzed.

In the U. K., no such murmur developed during the year in group A cases. In group B, where the murmur was initially absent, it appeared in only a few cases, equally in all treatment groups. Where it was initially present, it persisted up to the thirteenth week to a greater extent in the aspirin group (9 of 17 cases) compared with ACTH (3 of 19) and cortisone (5 of 18). At one year, however, there was little difference between the three groups (1 of 17 ACTH, 3 of 18 cortisone and 3 of 16 aspirin). In group C cases where the murmur was initially absent, it appeared in a few cases in all treatment groups by the end of one year. Where the murmur was initially present, it persisted in all treatment groups at the ninth week (13 of 20 ACTH, 12 of 19 cortisone and 15 of 19 aspirin) becoming slightly less at one year (9, 10 and 9 cases, respectively).

Presystolic Murmurs: Apical presystolic murmurs were not included in this analysis as they result from slowly progressive scarring of the mitral valve and are not evidence of acute carditis. In this study, they were present in only 16 of 497 cases (3.2 per cent) on admission and they appear for the first time in very few (12 additional cases during the following 13 weeks).

Summary of Murmurs. Summarizing the effects of treatment on murmurs during the acute attack and at the end of the first year, the following conclusions appear justified:

1.—The development of an apical systolic murmur among those without such murmurs at start of therapy, regardless of the presence or absence of carditis, was infrequent and was not related to the treatment.

2.—The disappearance of softer apical systolic murmurs was more rapid among those receiving ACTH or cortisone than among those receiving aspirin, but at the end of one year the treatment groups did not differ significantly. Similar results were found for the apical mid-diastolic murmur for the U. K. centers only.

3.—The disappearance or diminution of loud apical systolic murmurs rarely occurred regardless of therapy.

4.—The appearance or disappearance of basal diastolic murmurs occurred in a relatively small proportion of cases and in 11 of 12 centers was not related to therapy.*

5.—At the end of one year, there was no evidence that the treatment groups differed in the frequency with which murmurs had appeared or disappeared.

Seriously Ill Cases

Cases here described as seriously ill are those with congestive failure, pericarditis, or both, present on admission or occurring during the 13-week period of treatment and follow-up, and those cases terminated by death during the one year period of this report.

Congestive Failure and/or Pericarditis. At the start of treatment, 23 of 162 ACTH, 15 of 167 cortisone and 10 of 168 aspirin cases had congestive failure (table 27). Among these cases, failure disappeared at about the same rate regardless of therapy. In all but one case in each treatment group failure disappeared by the thirteenth week. After initial disappearance, it reappeared in only three cases, all in the ACTH group.

Among the cases *without* congestive failure at the start of therapy, 7 of 139 ACTH, 7 of 152 cortisone and 10 of 158 aspirin cases developed failure during the 13-week period (table 27). In 21 of these (seven ACTH, six

* In the one U. K. center where an abnormally high proportion of basal diastolic murmurs was heard at entry, they disappeared more frequently in the ACTH group.

ortisone and eight aspirin), failure appeared uring the treatment period but disappeared in l but five cases during the observation period. ne of these, a cortisone case, had fatal outome during the observation period and four wo ACTH, two aspirin) had persistent failre at the ninth week. In three cases (one CTH, two aspirin) failure was present at he thirteenth week. In one of these aspirin ases treatment had been changed to ACTH on he twenty-eighth and continued to the seventeth day.

Thus, among the cases with or without failure at the start of therapy, there were no marked differences among the treatment groups in the behavior of congestive failure.

Pericarditis was present at the start of therapy in 13 of 162 ACTH, 16 of 167 cortisone and 9 of 168 aspirin cases, and disappeared at approximately the same rate regardless of therapy (table 28). In only four of these (two cortisone and two aspirin) did the symptom reappear following its disappearance.

Among the cases *without* pericarditis at the start of therapy (table 28), there were 3 of 149 ACTH, 3 of 151 cortisone and 5 of 159 aspirin cases which developed pericarditis for the first time during the 13-week period. In nine of these (three ACTH, two cortisone and four aspirin), pericarditis appeared during the treatment period. In all 11 cases, it was of short duration, persisting in no case until the ninth week, and never reappearing after disappearance.

Thus, among cases with or without pericarditis at start of therapy, it appeared and disappeared regardless of treatment.

Deaths. Among the 497 cases, six deaths occurred during the one year of follow-up. Their case histories were as follows:

1.—A 12 year old girl was admitted to a U. K. center in her first attack, with fever, carditis with apical systolic murmur and gallop rhythm, erythema marginatum and elevated sedimentation rate. She was treated with ACTH on the twenty-fourth day of her disease, with symptomatic improvement but with progressive carditis. A basal diastolic murmur, noted intermittently during the first week of treatment, later was constantly present, becoming associated with a basal systolic murmur. In the fourth week an apical mid-diastolic murmur was heard and nodules appeared, rapidly increasing in number. The acute disease was obviously not controlled by ACTH. No additional symptoms appeared during the three-week observation period.

TABLE 27.—*Congestive Failure: U. K. and U. S., All Cases*

Interval from Start of Therapy in Days	Cases with Failure at Start of Therapy			Cases Without Failure at Start of Therapy		
	Number with failure present on first day of interval			Number developing failure for first time during interval		
	ACTH	Cortisone	Aspirin	ACTH	Cortisone	Aspirin
1–7	23	15	10	4	3	2
8–14	18	12	9	—	1	5
15–21	13	10	5	2	1	—
22–28	9	4	3	—	1	1
29–35	6	4	3	1	—	—
36–42	5	4	3	—	—	—
43–49	5	3	1	—	—	1
50–56	3	3	1	—	—	—
57–63	4 (1)	1	1	—	1 (died)	—
64th day	2	1	1	—	—	—
13th week	3 (2)	1	1	—	—	1

Figures in parentheses indicate number of cases on given day in which failure had reappeared after previous disappearance.

TABLE 28.—*Pericarditis: U. K. and U. S., All Cases*

Interval from Start of Therapy in Days	Cases with Pericarditis at Start of Therapy			Cases Without Pericarditis at Start of Therapy		
	Number with pericarditis present on first day of interval			Number developing pericarditis for first time during interval		
	ACTH	Cortisone	Aspirin	ACTH	Cortisone	Aspirin
1–7	13	16	9	1	1	1
8–14	8	8	7	2	—	2
15–21	3	6	3	—	—	—
22–28	2	5	3 (1)	—	—	—
29–35	1	3	3 (1)	—	—	1
36–42	1	2	1	—	1	—
43–49	1	2	1	—	—	1
50–56	1	—	1	—	1	—
57–63	—	1 (1)	—	—	—	—
64th day	—	1 (1)	1 (1)	—	—	—
13th week	—	—	—	—	—	—

Figures in parentheses indicate number of cases on given days in which pericarditis had reappeared after previous disappearance.

The patient was kept in bed thereafter throughout her slow but progressive downhill course, death occurring five months after the beginning of treatment, and one day following her removal from the hospital against advice.

2.—A 7 year old boy with a four-day history of precordial, pleural and joint pains, was admitted to his local hospital where his sedimentation rate was found to be elevated and a diagnosis of rheumatic fever made. He was treated with penicillin, sulfonamides and 4 Gm. of aspirin and 2 Gm. of sodium bicarbonate a day for 12 days without improvement. During this period he is said to have developed "a murmur" of gradually increasing loudness. He became dyspneic and was transferred to a U. S. center. On admission he was extremely ill, with fever, orthopnea, dyspnea, cyanosis, muffled heart sounds, apical systolic murmur, gallop rhythm and tachycardia (146 per minute). Bronchial breathing and rales were heard over both lung fields. A diagnosis of rheumatic pancarditis with mitral valvular disease and congestive heart failure was made and rheumatic pneumonia suspected. The patient was treated with digitalis and Thiomerin, and admitted to the study in the cortisone group. He died 20 hours after admission, having received 300 mg. of cortisone. Autopsy revealed a large, flabby heart with verrucae on the mitral valve and left auricular wall.

3.—A 13 year old girl with a previous history of rheumatic fever and rheumatic heart disease with mitral insufficiency was admitted to a U. S. Center on the fifth day of a recurrent attack, following an upper respiratory infection with sore throat of three weeks duration. She was moderately ill with fever, polyarthritis, elevated sedimentation rate and probable carditis. She was treated with cortisone for six weeks with a fairly satisfactory response, although the evidence of underlying rheumatic heart disease was unchanged. Two weeks following end of treatment, she suddenly, for the first time, went into congestive failure associated with elevated temperature and erythrocyte sedimentation rate. Retreatment with cortisone was begun immediately but she became rapidly worse and died one day later on the fifty-seventh day after admission to the study.

Autopsy revealed a greatly hypertrophied heart with obliteration of the pericardial cavity and chronic mitral disease without stenosis; bilateral pleural effusions; diffuse pulmonary edema and ascites. Microscopic examination showed evidence of diffuse active pancarditis.

4.—A 9 year old boy was admitted to a U. K. center with a history of three weeks of polyarthritis with two weeks of rash. He was found to have fever, erythema marginatum, an enlarged heart and a loud apical systolic murmur. He was admitted to the study and aspirin therapy begun. After slight improvement, his temperature rose again, the heart shadow became enlarged and a basal diastolic murmur was heart intermittently. At the end of nine weeks, he was still considered to be seriously ill and was transferred to another hospital, where he developed increasing congestive failure, which later stabilized and then gradually improved. Four months after start of treatment, while still hospitalized, he became febrile and a group A beta hemolytic streptococcus was isolated from his throat. He was treated with penicillin but remained febrile for 12 days, after which his temperature returned to normal but signs of congestive failure progressively increased. The patient died one month after this relapse, five months after start of treatment.

Autopsy revealed rheumatic endocarditis myocarditis, cardiac dilatation, a bicuspid aortic valve (? congenital), and chronic venous congestion of lungs, liver and spleen.

5.—A 12 year old boy was admitted to a U. K. center in his second attack with pre-existing rheumatic heart disease with mitral stenosis. Rheumatic fever had continued without intermission for four months manifesting itself by nodules, arthritis, erythema marginatum, precordial pain and fever. Physical findings during that period were enlarged heart, apical systolic, mid-diastolic, presystolic and basal diastolic murmurs, enlarged liver, pulmonary congestion, elevated sedimentation rate and prolonged P-R interval. The patient was admitted in the aspirin group, received symptomatic benefit, followed by relapse at the end of treatment. Four additional courses of aspirin were given, the patient responding in the same way each time. He was then placed on a cortisone schedule but showed no improvement, dying in the fifth week of this treatment, in congestive failure, eight months following admission to the study.

Autopsy revealed rheumatic heart disease with enlarged heart, mitral stenosis, acute mitral and tricuspid endocarditis, Aschoff bodies and fibroid changes in the myocardium, congestive failure with pulmonary edema, and cardiac cirrhosis of the liver.

6.—A 6 year old boy was admitted to a U. K. center, severely ill in the seventh week of his first (?) attack. He showed evidence of carditis with apical systolic and mid-diastolic murmurs and the signs of congestive failure. One subcutaneous nodule was noted on the right elbow. The temperature was normal and the erythrocyte sedimentation rate elevated. Because of intractable vomiting, the digitalis and aspirin were temporarily stopped late in the first week with immediate improvement. At the beginning of the second week, small doses of aspirin (1.2 Gm. per day) were given for three days and then omitted because of lack of improvement from therapy. The patient gradually improved without treatment but congestive failure persisted. During the fifth and sixth weeks, aminopyrin (0.5 Gm. per day) was given without effect on the patient's gradual improvement which continued

ntil the ninth week. Digitalis was then stopped nd the patient discharged to a convalescent home.

The patient continued in moderate congestive ailure, leading a bed and chair existence. Five nonths later, he developed an upper respiratory in- ection, treated with sulfamethazine and penicillin. 'achycardia (145 per minute) and a pericardial riction rub developed. A six week course of ACTH vas given with disappearance of acute symptoms, ongestive failure continuing. The patient had a apid increase in weight, marked moonface and noderate hypertension, all of which gradually dis- ppeared.

Ten months after admission to the study, the atient developed another upper respiratory infec- ion, treated with sulfonamide drugs and penicillin. He then went rapidly downhill and was transferred back to the center where he died in severe congestive failure after one week's treatment with ACTH, digitalis and diuretics.

Autopsy showed hypertrophy and rheumatic pneumonia, congestive failure with mitral stenosis, cardiac dilatation, acute and chronic lesions of mitral, aortic and tricuspid valves, fibrinous peri- carditis and numerous Aschoff bodies.

In summary, there were no appreciable differences in the course of seriously ill cases, since the behavior of congestive failure, pericarditis, or both, appeared to be similar in the treatment groups, and there were only six deaths (one on ACTH, two on cortisone and three on aspirin).

Retreatments

Apart from the six patients who died, there were some in each treatment group who, during the one year period, were retreated for persisting or recurring manifestations. Thus, retreatment was given to 10 of the 161 ACTH cases surviving to one year. None of these was given during the three-week observation period. One was treated for chorea, and one had two courses of retreatment. In all except the case with chorea, the symptoms demanding retreatment were moderately severe.

Retreatment was given to eight of the 165 cortisone cases surviving the one year, one of which was retreated during the observation period. All were moderately severe cases except one, having only erythema marginatum and fever. None was retreated for chorea. One case required two retreatments.

Retreatment was given to 19 of 165 aspirin cases surviving to one year. Four were retreated during the observation period, two receiving aspirin and the other two receiving cortisone. Thirteen of the 19 cases were moderately severe; of the remaining six, five were retreated for recurrent chorea and one for a mild illness consisting of elevated temperature and sedimentation rate.

When the cases given retreatment are analyzed according to duration of disease at start of therapy, it is seen that the differences among the three treatment groups are due entirely to the chronically ill cases. Thus, in the 0 to 14 day group, there were six ACTH, four cortisone and six aspirin cases to which retreatment was administered. In the 15 to 42 day group, the cases were two, one and four, respectively, and in the group of those ill 43 days or more, they were two, three and nine, a preponderance of aspirin cases in this chronically ill group.

Excluding the cases retreated for chorea, the number of cases remains the same in the 0 to 14 day group, becomes one on each treatment in the 15 to 42 day group, and two ACTH, three cortisone and seven aspirin in the 43 plus days group.

In summary, retreatment was given to a greater proportion of cases in the aspirin than in the ACTH or cortisone groups, but this difference occurred only among the chronic cases and was slightly affected by the larger number of cases initially admitted with chorea to the aspirin group.

Side Effects of Treatment

In both countries, practically all the ACTH and cortisone cases showed one, or a combination, of the following side effects of therapy: moonface, hirsutism, acne or striae. There were only 10.5 per cent of the ACTH and 4.8 per cent of the cortisone cases with none of these side effects by the end of the ninth week (table 29). These effects were recorded less frequently in the U. K. than in the U. S. cases, being absent in 15.0 per cent of the U. K. and 6.1 per cent of the U. S. ACTH cases, and in 10.0 per cent of the U. K. and none of the U. S. cortisone cases.

There were no appreciable differences between the ACTH and cortisone cases in frequency of moonface, hirsutism or striae, but

TABLE 29.—*Side Effects of Therapy in ACTH and Cortisone Cases: U. K. and U. S., All Cases*

Side Effect	Percentage of Cases Showing Side Effect					
	ACTH			Cortisone		
	U. K.	U. S.	Total	U. K.	U. S.	Total
Moonface	77.5	90.2	84.0	80.0	96.6	88.6
Hirsutism	15.0	19.5	17.3	13.8	16.1	15.0
Acne	26.2	63.4	45.1	8.8	17.2	13.2
Striae	12.5	12.2	12.3	18.8	12.6	15.6
None	15.0	6.1	10.5	10.0	0.0	4.8
Total number of cases	80	82	162	80	87	167

acne appeared much more frequently among the ACTH cases. With the exception of striae, each side effect was recorded more frequently among the U. S. than among the U. K. cases. Although these side effects appeared almost equally in the hormone groups, those severe enough, in the opinion of the investigator, to require stopping treatment occurred only among the ACTH cases (table 1).

In addition to the side effects of hormone treatment already noted, many others were reported, but not being specifically requested, they were not uniformly recorded. These included cases of hypertension, mental symptoms, convulsions, renal hemorrhage, water and salt retention, glycosuria, infections, hepatomegaly, febrile reactions, pigmentation, increased fat deposition and unusual increase in appetite.*

Relatively few aspirin cases developed side effects, and these all appeared in the first week of therapy in both countries while the dosage was relatively high. In the U. K., among 80 cases there were 4 with tinnitus or deafness, 7 with nausea and 1 with hyperventilation. Comparable figures in the 88 U. S. cases were 9, 19 and 5. The few side effects and the maintenance of the dosage schedule of aspirin without interruption, except in a rare case, suggests that these cases did not receive the maximum tolerated dosage.

In summary, very few patients in the hormone groups did not exhibit one or more side effects. Further, there was little difference between U. S. and U. K. cases on differing schedules of ACTH or between those on ACTH and those on cortisone in either country (table 29). In other words, the dosages of both hormones were large enough to produce a recognizable side effect in nearly all cases.

DISCUSSION AND CONCLUSIONS

The object of the present cooperative study, set up in 1950, was to measure the relative effects of ACTH, cortisone and aspirin when given uniformly in all centers according to defined schedules. These schedules (dosage, periods of administration and auxiliary therapy) were based mainly upon existent knowledge regarding apparent efficacy and toxicity. They had also to be practicable, not only in the length of time that patients could be kept in hospital during the trial itself, but to allow their subsequent application in medical practice if they proved to have value. It is obvious that innumerable other studies could be designed employing larger (or smaller) dosages, longer (or shorter) periods of treatment or individualized dosage schedules which would need to be based on predetermined criteria for changes in dosage. It cannot be maintained that such other schedules are either more or less effective than those used here without adequate controlled study.

Evaluation of treatment of such a complex and not wholly understood disease as rheumatic fever poses a large number of problems. Acute rheumatic fever may be considered a specific type of generalized inflammatory reaction but no means are available for measuring this quantitatively. Since it is impossible to correlate the observed manifestations with the severity of the pathological process, it must be accepted that the available data may represent only approximate indices of the severity of the disease. Furthermore, since many of the clinical evaluations are subjective, their interpretation must take into account observer error and acuity. For example, although there

* With an initial average body weight of a little less than 70 pounds in each treatment group, patients on ACTH and cortisone gained by the end of the ninth week an average of 11.3 and 11.8 pounds, whereas those on aspirin gained an average of 4.3 pounds.

general agreement as to the importance of apical mid-diastolic murmurs as an index of carditis, inconsistencies in reporting them and difficulties in distinguishing them from a third heart sound or gallop rhythm gave this index uncertain value in this study. In general, such difficulties were reduced by the large number of patients in each treatment group and by the equal allocation of the three drugs within each study center.

Other difficulties encountered in the evaluation of certain data were the lack of normal standards and the absence of normal values to serve as base lines at the start of therapy. Moreover, variables which have been analyzed separately may be interdependent. An example of these difficulties is interpretation of the changes in P-R intervals with changing pulse rates and heart size.

In addition to grouping by duration of disease, various types of classifications of patients were made. The most useful was based on the presence or absence of cardiac involvement on admission to the study. Owing, however, to the random allocation of patients to treatment and the consequent balance of characteristics, such additional groupings had roughly equal numbers in the three treatment groups. Each manifestation was analyzed in several ways and that method chosen for presentation, which gave the clearest picture.

It should be noted that nowhere in this report have analyses of combinations of measurements and clinical signs been presented. Since in clinical practice the patient is assessed as a whole, attempts were made to integrate the separate manifestations in individual patients. These attempts were unsuccessful in providing new information, but observing each case over the entire 6 to 9 week observation period, the proportion without any manifestation of rheumatic fever was found to be greater in the aspirin than in either of the hormone groups. This difference was observed whether or not a murmur at this time (6 to 9 weeks) was considered to be a manifestation. Thus, including a murmur as a manifestation, there were with no manifestations at all, 11 cases on ACTH, 11 on cortisone and 25 on aspirin. This difference, however, is almost entirely due to the smaller proportion with an elevated erythrocyte sedimentation rate and/or raised pulse rate among the cases in the aspirin group. Adding the cases with only these signs to the group showing no manifestations, the numbers of the latter become 34 on ACTH, 32 on cortisone and 34 on aspirin. If the presence of a murmur at this time (6 to 9 weeks) is not regarded as a manifestation, the numbers with no manifestations during the whole 6 to 9 week period were 31 on ACTH, 26 on cortisone and 53 on aspirin. Adding to these the cases with only an elevated erythrocyte sedimentation rate and/or raised pulse rate, the figures become 71 on ACTH, 62 on cortisone and 72 on aspirin.

In attempting to assess the relative efficacy of ACTH, cortisone and aspirin in altering the acute disease or suppressing its manifestations, the following conclusions appear permissible.

1.—During the acute illness and the first year of follow-up, very few deaths occurred, one in the ACTH, two in the cortisone and three in the aspirin group. Retreatments were given to some cases in all three groups, but apart from a slight excess in the late-treated cases on aspirin, there was no marked difference in the groups.

2.—The temperature and pulse rate during sleep returned to normal during treatment in the great majority of cases in all treatment groups, but there was a greater tendency in the groups treated with the hormones for the rates to become elevated in the 6 to 9 week observation period.

3.—The erythrocyte sedimentation rate decreased more rapidly during treatment in the hormone treated groups but was elevated more frequently in the 6 to 9 week observation period. There were no differences between the treatment groups at the thirteenth week.

4.—The behavior of joint involvement, chorea and erythema marginatum was essentially the same in the three treatment groups. Nodules, however, disappeared more rapidly in the patients treated with ACTH and cortisone although new nodules appeared in some patients during treatment in all three groups.

5.—The analysis of the effects of the drugs on carditis, while undoubtedly most important, is

especially difficult and the conclusions the least clear. The following, however, seem justified:

a. There appeared to be no relationship between the treatment given and the behavior of congestive failure and pericarditis.

b. There was more frequently an increase in heart size as measured by a change of 0.6 cm. or more in each of the hormone groups as compared with the aspirin group. This may be related to a possible increase in blood volume or in some cases to abdominal distention. It was not related consistently to weight gain since heart size increased frequently in the 0 to 3 week period of treatment and much less frequently in the observation period (6 to 9 weeks) although the average weight gain during these two periods was very similar. At the one-year follow-up examination, there was no appreciable difference between the three groups.

c. The appearance for the first time of apical systolic murmurs was infrequent in all three treatment groups and unrelated to therapy. No consistent difference in the behavior of murmurs present at the start of treatment was noted except that the soft apical systolic murmurs disappeared more rapidly in hormone treated groups. At the end of one year, however, no significant difference remained. The differences in the treatment groups with respect to apical mid-diastolic murmurs in the U. K. and basal diastolic murmurs at one U. K. center have been discussed.

d. The P-R intervals decreased more frequently and more rapidly in the hormone groups than in the aspirin group. This difference between the groups lessened during the observation period and was absent at nine weeks and one year. Since the values at these later times might be closer to normal than those recorded during acute illness, it may be questioned whether the early decrease is an effect of the hormones on the disease or merely a direct effect on atrioventricular conduction time.

e. At one year the proportion with residual cardiac damage was similar in the three treatment groups. A final determination of cardiac status must await results of a prolonged follow-up.

It is apparent that this study presents no evidence that rheumatic fever in children can be uniformly terminated by any of the three agents. There is evidence that hormone treatment results in more prompt control of certain acute manifestations, but this more rapid disappearance is balanced by a greater tendency for them to reappear for a limited period of time at the end of treatment. Treatment with the hormones also leads to the more rapid disappearance of nodules and of soft apical systolic murmurs. At the end of one year, however, it is clear that there was no significant difference between the treatment groups in the status of the heart.

Summary

1.—Six centers in the United Kingdom, five in the United States and one in Canada have collaborated in a trial of the relative merits of ACTH, cortisone and aspirin in the treatment of acute rheumatic fever and the prevention of rheumatic heart disease. The present report relates to children under the age of 16 and compares the effects of the three drugs on the acute course of the disease and on the persistence and development of rheumatic heart disease through one subsequent year.

2.—The records of 497 patients are presented (240 U. K. and 257 U. S., including the Canadian center in the latter). Each case met specified diagnostic criteria on admission to the trial and was allocated at random to treatment with one of the three drugs. Each treatment was given for six weeks according to a defined schedule and detailed observations were continued for a further three weeks. Follow-up examinations were made at specified times after these nine weeks and the present report extends to the examination made one year later, i.e., 61 weeks from the start of treatment.

3.—The study was designed to insure a balance of cases in the three treatment groups for each center, for the duration of illness at start of treatment and for the time of year when cases were admitted. Random allocation

of cases within this balanced design was relied upon to secure a reasonably equal distribution of cases according to age, sex, severity and frequency of manifestations of disease. This design permits many comparisons of the total groups on each treatment.

4.—In 51 per cent of the patients, treatment was begun within 14 days of the onset of the attack; in nearly two-thirds there was no history of a previous attack or evidence of pre-existing rheumatic heart disease. The treatments were, therefore, tested on patients of whom a large proportion were still in the early stages of the disease and had no established heart disease.

5.—The three randomly constructed groups on ACTH (162 cases), cortisone (167 cases), and aspirin (168 cases) were notably alike in most respects at the start of the trial. The results of the treatments were measured in relation to separate manifestations of the disease, viz., temperature, pulse rate during sleep, erythrocyte sedimentation rate, joint involvement, chorea, erythema marginatum, nodules and such aspects of the status of the heart as heart size, atrioventricular conduction time, murmurs, and, in particular, those indicative of serious illness, namely, congestive failure and pericarditis.

6.—There was no evidence that any of the three agents resulted in uniform termination of the disease and on all treatments some patients developed fresh manifestations during treatment. Treatment with either of the hormones resulted in more prompt control of certain acute manifestations but this more rapid disappearance was balanced by a greater tendency for the acute manifestations to reappear for a limited period upon cessation of treatment. Treatment with the hormones also led to more rapid disappearance of nodules and soft apical systolic murmurs. At the end of one year there was no significant difference between the three treatment groups in the status of the heart. During the period of treatment, observation and one year of follow-up there were only six deaths among the 497 cases under the age of 16, admitted to this study.

Acknowledgment

Grateful acknowledgment is made to the resident and technical staffs at the cooperating centers, without whose devoted efforts the collection of these data would have been impossible.

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APPENDIX

Study Form 1

1. Hosp. No..... **Admission Report** 2. Study No.....

3. Study center..... 4. Date adm. to center..... 5. Date therapy begun.....
6. Name of patient..... 7. Date of birth..... 8. Age..... 9. Sex..... 10. Race.....

Major Manifestations	Has condition been present in this attack	Date first observed in this attack	Is condition present at start of therapy	Acceptable as criterion for admission to study
11. Active carditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
a. Development of or change in murmurs	Yes ☐ No ☐	.....	Yes ☐ No ☐	
b. Increase in heart size	Yes ☐ No ☐	.....	Yes ☐ No ☐	
c. Pericarditis	Yes ☐ No ☐	.....	Yes ☐ No ☐	
d. Congestive failure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(1) Dyspnea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(2) Orthopnea	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(3) Liver enlargement	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(4) Rales	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(5) Increased jug. ven. pressure	Yes ☐ No ☐	.....	Yes ☐ No ☐	
(6) Edema	Yes ☐ No ☐	.....	Yes ☐ No ☐	
12. Polyarthritis (2 or more joints)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
13. Chorea (definite)	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
14. Nodules	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐
15. Erythema marginatum	Yes ☐ No ☐	.....	Yes ☐ No ☐	Yes ☐ No ☐

Minor Manifestations				Max. measurement in present attack	
16. Fever	Yes ☐ No ☐	.....	Yes ☐ No ☐	.....	Yes ☐ No ☐
17. Elevated ESR (15 mm./hr or over, corrected Wintrobe)	Yes ☐ No ☐	.....	Yes ☐ No ☐	.....	Yes ☐ No ☐
18. Previous strep. infection	Yes ☐ No ☐	.....			Yes ☐ No ☐
a. Positive culture	Yes ☐ No ☐	.....			
b. ASO titer		.....		.....	
c. Sore throat with fever	Yes ☐ No ☐	.....			
19. Increased P-R interval	Yes ☐ No ☐	.....	Yes ☐ No ☐	.....	Yes ☐ No ☐
20. Previous history of rheumatic fever or rheumatic heart disease:					Yes ☐ No ☐

(a) Total No. of attacks including present attack..... Reliability of history Good ☐ Questionable ☐ Poor ☐

(b) Date 1st attack.....Manifestations.....

Date 2nd attack.....Manifestations.....

Date 3rd attack.....Manifestations.....

(c) Residual heart damage from these or any unrecorded attacks:

(1) History of .....

(2) Present findings .....

21. Previous Therapy	Date begun	Total amt. given	Date stopped
ACTH (any attack)	.....	.....	.....
Cortisone (any attack)	.....	.....	.....
Salicylates (this attack)	.....	.....	.....

Summary

22. General description of patient's condition and course and severity of attack:

.....

.....

.....

.....

.....

.....

23. Present diagnosis Anat.....

Physiol. .....

24. Date onset (present attack).....

25. Study group (check box below)

Duration from onset	Age: Under 16 yrs.	Age: 16 yrs. and over
0-14 da		
15-42 da		
43 da and over		

26. Therapy group: ACTH ☐ Cort. ☐ Salic. ☐
Excluded from study ☐
(If case was excluded from study explain fully on back of form)

27. Investigator (sign.) .....

28. Date reported to center.....

COOPERATIVE RHEUMATIC FEVER STUDY

American Council on Rheumatic Fever — Medical Research Council of England

Form 1

Study Form 2, part 1

Hospital No. _____ Name of Patient _____ Address _____ Birth Date _____ Sex _____ Study No. _____

Progress Report No._____

Date of beginning of this record sheet _____

Date of end of this record sheet _____

Principal investigator (Sign) _____

Date signed _____

COOPERATIVE RHEUMATIC FEVER STUDY
American Council on Rheumatic Fever — Medical Research Council of England

Form 2

Study Form 2, part 2

1. Hosp. No. ______________ **Progress Record Sheet No.** ____ 2. Study No. ______________

3. Study center ______________ 4. Date adm. to center ________ 5. Date therapy begun ________
6. Name of patient ______________ 7. Age ______ 8. Sex ______ 9. Race ________

	10. (a) Date (month and day)																					
	(b) Days from onset																					
	(c) Day of therapy																					
General	11. Temp. (highest for day)																					
	12. Sleeping pulse																					
	13. Weight																					
	14. Blood pressure																					
Heart	15. Gallop																					
	16. Arrhythmias																					
	17. Murmurs																					
	a. Apical organic systol.																					
	b. Apical mid diastolic																					
	c. Basal diastolic																					
	d. Apical presystolic																					
	18. Precordial pain																					
	19. Pericardial (a) rub																					
	(b) effusion																					
	20. Failure																					
	a. Orthopnea																					
	b. Dyspnea																					
	c. Liver enlargement (cm)																					
	d. Edema																					
	e. Rales																					
	f. Jugular venous press.																					
	g.																					
	21. (a) TD/ID																					
	(b) Contour																					
	22. PR/Vent. rate																					
	23.																					
	24.																					
Other	25. Joint involvement																					
	26. Nodules																					
	27. Erythema marginatum																					
	28. Chorea																					
	29.																					
	30.																					
Laboratory	31. ASO Titer																					
	32. ESR (uncorrected)																					
	33. Hematocrit																					
	34. Eosinophiles																					
	35. pH																					
	36. CO_2 (meq.)																					
	37. K (meq.)																					
	38. Urine sugar																					
	39.																					
	40.																					
Therapy	41. A C S 24 hr. dosage																					
	No. doses/day																					
	42. KCl added																					
	43. Digitalis																					
	44.																					
	45.																					
	46. Chemotherapy																					
	47. Toxic symptoms																					
	48. Complications																					
	49. Gen'l cond. of patient																					

Study Form 2, part 3

Progress Notes

Date	Notes	Observer
	Weekly Summary of General Condition of Patient	

Study Form 2, part 4

1. Hosp. No._____ 2. Study No._____

Side Effects of Therapy

3. Study center_____ 4. Date adm. to center_____ 5. Date therapy begun_____
6. Name of patient_____ 7. Age_____ 8. Sex_____ 9. Race_____

Symptom	Date of 1st Appearance	Date of Disappearance	Describe Severity
10. Moonface			
11. Abnormal fat deposition			
12. Hirsutism			
13. Acne			
14. Striae			
15. Amenorrhea			
16. Mental changes (specify)			
a.			
b.			
c.			
d.			
17. Weakness			
18. Pigmentation			
19. Other (specify)			
a.			
b.			
c.			
d.			
20. Salicylism (specify)			
a.			
b.			
c.			
d.			
e.			

Study Form 37

1. Study No. _____

Evaluation Report

2. Study center _____ 3. Date adm. to study _____

4. Name of patient _____ 5. Date of last evaluation _____

History Since Last Evaluation

6. Working or attending school: Yes ☐ No ☐

7. a. At home No. of days _____ Dates _____
   Reason _____
   b. In hospital No. of days _____ Dates _____
   Reason _____
   c. In conv. home No. of days _____ Dates _____
   Reason _____

8. Prophylactic regime followed
   a. Well (6-7 days per week) ☐
   b. Poorly (5 or less days per week) ☐
   c. Urine test _____ Blood test _____

9. Observations and complaints since last evaluation (Amplify on reverse items checked "Yes")

a. Fever	Yes ☐	No ☐	Dates _____
b. Coryza	Yes ☐	No ☐	Dates _____
c. Sore throat	Yes ☐	No ☐	Dates _____
d. Swollen glands	Yes ☐	No ☐	Dates _____
e. Rash	Yes ☐	No ☐	Dates _____
f. Nose bleed	Yes ☐	No ☐	Dates _____
g. Chest pain	Yes ☐	No ☐	Dates _____
h. Abdom. pain	Yes ☐	No ☐	Dates _____
i. Vomiting	Yes ☐	No ☐	Dates _____
j. Anorexia	Yes ☐	No ☐	Dates _____
k. Dyspnea	Yes ☐	No ☐	Dates _____
l. Orthopnea	Yes ☐	No ☐	Dates _____
m. Joint pains	Yes ☐	No ☐	Dates _____
n. Nodules	Yes ☐	No ☐	Dates _____
o. Chorea	Yes ☐	No ☐	Dates _____
p.			Dates _____

10. Therapy since last evaluation (Specify on reverse how given, dates and amounts)

a. Aspirin	Yes ☐	No ☐
b. ACTH	Yes ☐	No ☐
c. Cortisone	Yes ☐	No ☐
d. Antibiotics	Yes ☐	No ☐

e. Other (specify) _____

11. Laboratory results (since last evaluation)

Dates	ESR (uncorr.)	Htc.	ASO
Present exam.			

Present Evaluation

12. X-Ray a. T.D. _____ b. I.D. _____ c. Effusion Yes ☐ No ☐
    d. Contour _____ e. Enlarg. Yes ☐ No ☐

13. ECG a. P.R. _____ b. V.R. _____ c. Other _____

Physical Examination

14. Height _____ 18. Chorea (Grade 0-3) _____
15. Weight _____ 19. Joints (Grade 0-3) _____
16. Temp. _____ 20. Nodules Yes ☐ No ☐
17. B.P. (supine) _____ 21. Rashes Yes ☐ No ☐
    (Amplify on reverse items 18-21)
22. Heart rate _____
23. Gallop Yes ☐ No ☐ Type _____
24. Rhythm _____
25. Friction rub Yes ☐ No ☐
26. P.M.I. _____
27. Thrills Yes ☐ No ☐
    Location _____ Time _____
28. M_1 accentuated Yes ☐ No ☐
29. P_2 accentuated Yes ☐ No ☐
30. Evidence of failure
    a. Dyspnea Yes ☐ No ☐
    b. Orthopnea Yes ☐ No ☐
    c. Rales Yes ☐ No ☐
    d. Liver enlg. Yes ☐ No ☐ cm. _____
    e. Edema Yes ☐ No ☐
    f. Inc. venous press. Yes ☐ No ☐
31. Murmurs (If "Yes", describe on reverse intensity, quality, duration, time in cycle, transmission)
    a. Mitral systolic Yes ☐ No ☐
    b. Mitral diastolic Yes ☐ No ☐
    c. Aortic systolic Yes ☐ No ☐
    d. Aortic diastolic Yes ☐ No ☐
32. Diagnosis: a. Etiol. _____
    b. Anat. _____
    c. Physiol. _____
    d. Func. and Ther. _____
33. Has there been rheumatic activity: None ☐
    Continued ☐ Exacerbated ☐ New attack ☐
    Evidence of severity _____
34. Significant change since last evaluation _____
35. Exam. by (sign) _____
    Date examined _____
36. Prin. Investigator (sign) _____

COOPERATIVE RHEUMATIC FEVER STUDY

American Council on Rheumatic Fever — Medical Research Council of England

Form 4

The Opening Snap of the Tricuspid Valve: A Physical Sign of Tricuspid Stenosis

By CHARLES E. KOSSMANN, M.D.

In two patients with rheumatic heart disease a short, loud, high pitched, early diastolic, snapping sound was heard at or below and to the right of the xiphisternum. Except for the different area of audibility it was similar on auscultation to the opening snap of the mitral valve. Both patients showed clinical evidence of tricuspid as well as mitral and aortic valvular disease. There was hemodynamic evidence of tricuspid disease in one, and the other displayed tricuspid stenosis at necropsy. The abnormal sound was regarded as the opening snap of the tricuspid valve.

THE precise clinical localization of structural valvular defects in the heart, and an exact estimation of the dynamic alterations caused by them have assumed considerable practical importance with the advent of surgical procedures for the correction of such defects. Among the more difficult of these to diagnose clinically is tricuspid stenosis. Since surgical treatment of it can be, and has been, successfully achieved,[1, 2, 3] any additional aid in its preoperative detection should be of more than academic interest.

Neither the normal mitral valve or the normal tricuspid valve make any sound on opening at the termination of isometric relaxation of the ventricles. Luisada[4, 5] has recorded a single vibration in normal subjects in early diastole which he regards as originating from the opening of the atrioventricular valves, but unlike the sound arising from pathological valves it is of low frequency. Disturbing, too, is that it may occur before the peak of the V wave in the jugular phlebogram. By contrast, the structurally deformed mitral valve was believed as early as 1872[6] to make a sound which has come to be known as the opening snap of the mitral valve.[7] It is short, of snapping quality, and occurs anywhere from 0.03 to 0.014 second after the beginning of the second heart sound.[8, 9] It is usually heard best in the region of the fourth rib at the left sternal border, but this may vary to include the pulmonic and left nipple regions of the precordium. Occasionally it may be heard elsewhere but never louder than in the regions noted. It is believed to be created by the opening of stiffened, not rigid, mitral leaflets. It has come to be regarded as being as pathognomonic of mitral stenosis as the apical diastolic rumbling murmur associated with this lesion.[8]

So far as could be determined, the first reference* to the creation of a sound by the diseased tricuspid valve was made by Rivero-Carvallo[10] who heard or recorded the "chasquido de apertura de la tricúspide" in 10 of 50 cases with tricuspid stenosis. No details were given although he pointed out that it was less intense, shorter, and sharper than the corresponding snap of the mitral valve, and could easily be confused with it if the latter were propagated toward the tricuspid region of auscultation. He published one example in which the opening snap was recorded only during a period of postinspirational apnea.

It is the purpose of this paper to describe two additional patients with this new physical

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Presented at the Second World Congress of Cardiology held in Washington, D. C., Sept. 16, 1954.

Aided in part by a grant of the Mona Bronfman Sheckman Foundation to Lenox Hill Hospital.

* The present author's initial observations were made late in 1952 and early in 1953 without knowledge of Rivero-Carvallo's paper. The latter was called to his attention by Dr. A. A. Luisada at the recent Second World Congress of Cardiology. He takes this opportunity to thank Dr. Luisada for pointing out the unintentional omission of this reference in the paper as presented.

sign, in both of whom the existence of tricuspid disease was clinically obvious, and in one of whom the lesion of tricuspid stenosis was proven at necropsy.

Case 1. E. S., a 34-year-old, single, white man, developed acute rheumatic polyarthritis after pneumonia at the age of 11 years. While still being observed in another hospital during the acute attack, evidence of mitral stenosis and mitral insufficiency developed.

He first came under our observation at the age of 15 years when the diagnosis of mitral valvular deformity was confirmed. He was seen regularly at the Cardiac Clinic. At 18 the basal diastolic murmur of aortic insufficiency appeared. In 1941, at the age of 20, the first symptoms of diminished cardiac reserve occurred. Active rheumatic carditis was suspected, and he was admitted to the hospital for the first time. However, the suspicion was not confirmed by the laboratory data accumulated.

At 21 years of age the first bout of atrial fibrillation occurred which was treated with quinidine. Between the ages of 21 and 26 years there were repeated attacks of palpitation documented on three additional hospitalizations as atrial fibrillation, and on several clinic visits as either this arrhythmia or normal sinus rhythm with atrial and ventricular premature systoles. Control was restored by manipulation of the dosage of quinidine, on one occasion preceded by temporary digitalization.

In the summer of 1946, when the patient was 26 years old, he was admitted for the fifth time to the hospital for his first bout of congestive heart failure. He was critically ill and the course was complicated by development of an atonic bladder and a small cerebral embolus with partial and transient paralysis of the right arm and the right side of the face. Rather large doses of digitalis were required to bring the ventricular rate under control. The fibrillation of the atria became permanent. At the end of five months he was well enough to return to the clinic on digitalis.

Except for the development of a renal infarct in October 1947, the patient was fairly well for the next four years, sometimes requiring as little digitalis as 0.05 Gm. five days per week.

In 1950 he began to have four to seven bowel movements a day. For this symptom he was studied on his seventh, eighth, and ninth admissions to the hospital between April 1951 and June 1952. Gastrointestinal reviews revealed only an enlarged liver which on biopsy revealed increased fibrosis suggestive of cirrhosis, and an elevated serum bilirubin 3.3 mg. per 100 cc.). Soon thereafter pulsation of the liver was noted, and tricuspid insufficiency was added to the diagnosis.

Late in 1952, when the patient was 32 years old, an early diastolic snapping sound was heard in the fourth right intercostal space 3 cm. lateral to the right sternal border. This tenth admission to the hospital was for palpitation and dyspnea as were the next three admissions, the last in February 1954. In each instance the patient was found to have a rapid ventricular rate, was quite ill, and was given additional digitalis either as ouabain or Digoxin intravenously despite the fact that he had been faithful in taking his "maintenance" dose. In each instance the ventricular rate was reduced quite promptly to acceptable levels at which palpitation disappeared. The fourteenth and fifteenth admissions were for special studies.

The *physical findings* varied over the years. At the time of most of the stethographic studies in 1953 and 1954 the cardiac examination revealed the following: There were three distinct impulses visible and palpable on the anterior thorax. The easiest to see was a systolic retraction in the right fifth intercostal space just medial to the nipple. The apex beat in the fifth intercostal space just beyond the left midclavicular line was also a retraction. Below this, the lower and outer point in the sixth intercostal space near the left anterior axillary line was palpable as a retraction but could not be seen. The third impulse was of the xiphoid itself which was thrust forward with systole in a visible, forceful manner. A long diastolic thrill was felt at the apex with the patient in the left lateral supine position. The first sound at the apex was poor; at the base the pulmonic second sound was louder than the aortic second but neither was unusually loud. A moderately loud blowing, transmitted systolic murmur and a long, holo-diastolic, decrescendo, rumbling diastolic murmur were audible at the apex. A soft systolic blow and a soft diastolic blow were heard along the lower left sternal border but no sound simulating the opening snap of the mitral valve could be heard in this area. In the aortic region there was a soft systolic blow also. At the xiphoid there was a loud, harsh, rasping systolic murmur transmitted upward and to the right and followed by an early diastolic rumble of different quality than the one at the apex. Upward and farther to the right near the fifth rib in the right parasternal line this murmur was blowing rather than rumbling in character. On the lower right anterior thorax in a roughly triangular area with its apex at the fifth rib in the right anterior axillary line and its base extending along the costal margin from the fifth rib in the midsternal line to the eighth rib in the anterior axillary line (figure 1, E. S.) there was a loud, snapping sound occurring immediately after the second sound and ascribed to the opening of a deformed tricuspid valve. The area of audibility indicated was that found in 1954. A year earlier it was farther to the left and included the xiphoid but did not extend beyond the left sternal border. The ventricular rate was approximately 50 per minute, and premature systoles with coupling were common. The blood pressure averaged 120/80,

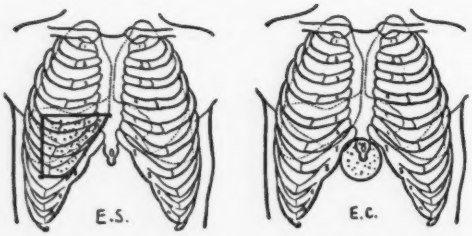

FIG. 1. Approximate areas (shaded) in which the opening snap of the tricuspid valve was heard in case 1 (E. S.) white male, age 34, and in case 2 (E. C.) white female, age 45. In case 1 the area is the one in which the snap was heard in 1954. A year earlier it could be heard farther to the left and lower near the xiphisternum. (See fig. 4.)

esophagus was displaced posteriorly and to the right. The hilar shadows were prominent.

Electrocardiograms were recorded frequently for 19 years. The changes which occurred may be seen in a record taken in 1940 and another in 1954 (figure 3). During this interval, in addition to the changes in rhythm, there was a gradual widening of the QRS interval to 0.11 second, and development of a form and axis of QRS deviated to the right ascribed to incomplete block of the right bundle-branch. There was on occasion a rapid ventricular rate at which time the QRS interval would usually be longer. In the record of 1940 the left deviation of the electrical axis of the P wave is to be noted.[11]

Stethograms were recorded on several occasions in 1953 and 1954. An example of one made on May

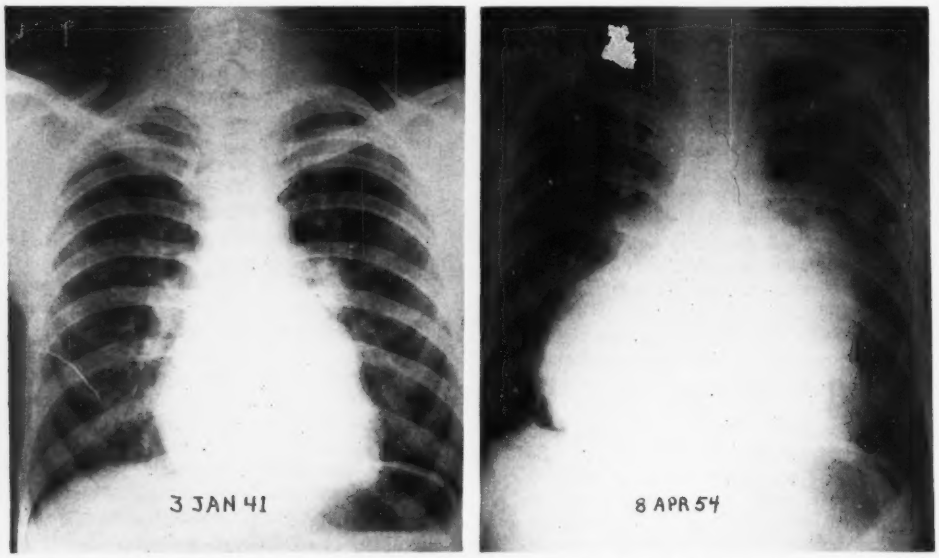

FIG. 2. Case 1 (E. S.). Teleroentgenograms made on Jan. 3, 1941 and 13 years later on April 8, 1954. The considerable enlargement to the right, the elongation of the right atrial curve, and the bulge of the middle of the left border which developed over the interval are to be noted. The right atrial enlargement is particularly suggestive of tricuspid valvular disease.

and for a good many years had varied between 90 and 130 systolic, and 60 to 90 diastolic. There were none of the usual peripheral phenomena of aortic insufficiency. However, both the large liver and the dilated jugular veins pulsated with systole. Although the spleen was enlarged it could not be felt to pulsate.

Roentgenograms. The change in the x-ray appearance of the heart over the years is demonstrated in figure 2. Fluoroscopy on many occasions disclosed evidence of marked enlargement of both atria, and of the right ventricle, less of the left ventricle. The

18, 1953 is shown in figure 4.* At this time, the opening snap could be heard farther to the left

* The stethograph of the Cambridge Instrument Co.[12] was used to make this and the record in figure 7. Its characteristics were not tested but its galvanometric response to sound waves is reported by the company as being approximately stethographic. The frequency response curve falls below 50 and above 600 cycles per second, and shows a peak at 400 cycles per second. Overall recording with amplifier and microphone in circuit causes some modification of the curve described.

ar the xiphoid than was the case in 1954 (figure 1). The simultaneous mechanical record is a right jugular phlebogram with the bifid appearance characteristic of tricuspid insufficiency when the auricula are fibrillating.[14] The records clearly show a second sound which begins 0.40 second after the beginning of the QRS interval (Q-2), a similar value being found in the basal record (0.41 second). On the other hand, the interval from the beginning of QRS to the beginning of the opening snap (Q-O.S.) is 0.53 second. Other phonocardiograms were made from other areas both by stethographic and logarithmic recording. One of these was calibrated, and revealed an intensity of the snap of approximately 86 decibels. A feature not revealed by auscultation was a split second sound in the pulmonic area. An opening snap of the mitral valve was not recorded.

The interval between the beginning of the second sound and the beginning of the opening tricuspid snap varied from 0.097 second to 0.129 second with a mean of 0.111 second (10 observations). It showed a general tendency to elongate when the preceding cycle was longer[9, 18] but the relationship in this patient was not definite. It was a little better when the interval between the highest peaks of the two sounds were used as reference points for the interval. Because of frequent premature systoles with coupling it was difficult to get many cycles uncomplicated by the arrhythmia.

*Cardiac catheterization** was attempted on April 7, 1954 and again nine days later. In each instance the voluminous right atrium was entered easily but with no amount of manipulation within the safe limits of the necessary fluoroscopic radiation was it possible to get the catheter's tip through the presumed button-hole tricuspid orifice. Success in this regard was undoubtedly thwarted further by a vigorous systolic jet, which during one set of observations carried the regurgitant pressure in the right atrium to 40 mm. Hg, with a diastolic pressure of 21 mm. Hg and a mean of 25 mm. Hg.

Atrial pressure pulses on another occasion were made simultaneously with an electrocardiographic lead (aV_F) and with a stethogram. The latter was recorded linearly after passing the sound through a filter with a band pass† of 400 to 800 cycles per second. The atrial pressure recorded by strain-gauge transduction, electronic amplification, and cathode-ray oscilloscopic visualization‡ showed a bifid systolic curve with a rapid fall in early diastole. A v wave could not be recognized but of possible significance in interpretation was that the opening snap occurred approximately 0.03 second after the pressure curve began rapid descent (dashed vertical lines in fig. 5) and 0.05 second after initial slower descent. Although much distortion of the pressure pulse probably exists, recorded as it was through a cardiac catheter,[15] nevertheless the abnormal sound occurred at an appreciable interval after a rapid fall in pressure began, and actually at a time when the steepest part of the curve had passed (see Discussion).

The similarity of the atrial pressure pulse to the jugular phlebogram (figure 4) and the hepatogram (figure 6) recorded by means of a piezo-electric microphone with linear displacement placed on the abdomen over the liver is to be noted.

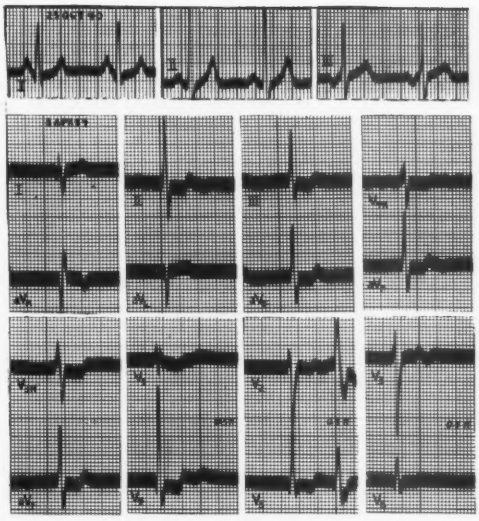

FIG. 3. Case 1 (E. S.). Bipolar leads I, II and III (top line) made on Oct. 23, 1940 when the patient was taking no medication. The P waves are broad and the axis of P deviated well to the left, but the record is not otherwise beyond normal limits. The lower two lines show electrocardiograms made on April 8, 1954 when the patient was taking digitalis. In each frame two electrocardiograms are recorded simultaneously. The symbols have the usual meaning.[20]

In the interval between records the electrical axis of QRS has deviated to the right, the QRS interval has increased to 0.11 second, and the form of the ventricular deflections in leads I, V_{4R}, V_{3R}, and V_1 suggest the presence of some block in the right bundle branch, and hypertrophy of the right ventricle. Records from the left side of the precordium show relatively high R waves. A ventricular premature systole occurred while recording leads V_2 and V_5.

Leads V_1 through V_6 (last three frames, lowest line) were made with the galvanometer at half normal gain (1 mv = 0.5 cm). Time lines, 0.04 second.

* The author had the indispensable help of Drs. Alfred Kaltman, Rejáne M. Harvey, and George Thomson in doing these studies.

† Filter on the Cambridge Instrument Company's Tape Recorder.

‡ Manufactured by Electronics in Medicine, New York.

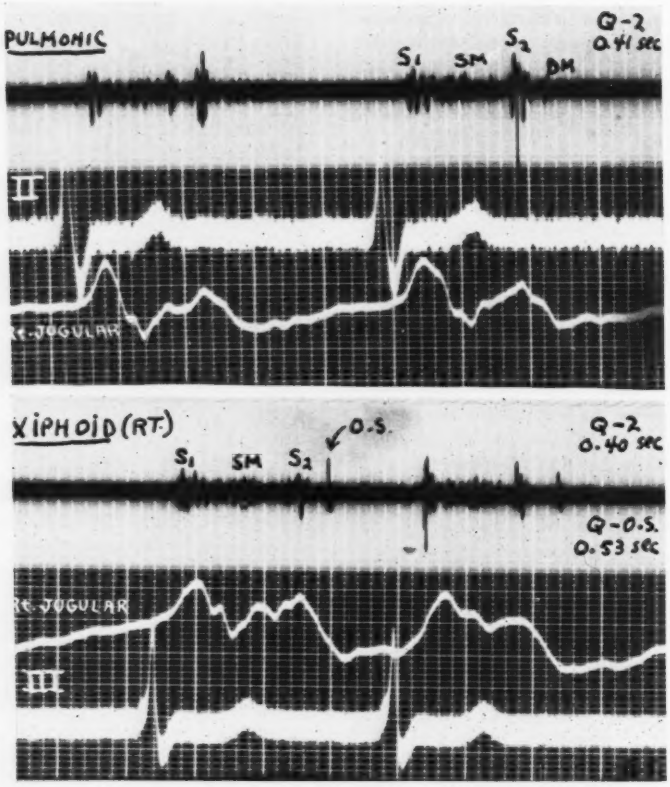

FIG. 4. Case 1 (E. S.). Stethograms made with the microphone in the pulmonic area simultaneous with the right jugular phlebogram and lead II (upper record), and with the microphone just to the right of the xiphisternum simultaneous with the right jugular phlebogram and lead III (lower record) on May 18, 1953. S_1, first sound; S_2, second sound; SM, systolic murmur; DM, diastolic murmur; O.S., opening snap. Q-2 and Q-O.S. are the intervals between the beginning of QRS and the beginning of the second sound (Q-2) and the beginning of the opening snap (Q-O.S.) respectively. The stethograms were made with a stethoscopic bell 5 cm. in diameter and equipment of the Cambridge Instrument Company. Volume controls were at six and eight respectively for the two records.

Limitation of the snap to the area of the xiphoid, and the bifid nature of the jugular phlebogram are to be noted.

Diagnosis. The patient was regarded as having chronically or recurrently active rheumatic heart disease with enlarged heart, mitral stenosis, mitral insufficiency, tricuspid stenosis, tricuspid insufficiency, aortic insufficiency, intracardiac thrombi, atrial fibrillation with frequent ventricular premature systoles, and congestive heart failure. Cerebral and renal infarction secondary to emboli had occurred in the past, and there was cardiac cirrhosis of the liver.

Case 2. E. C., a 45 year old white married housewife, did not know of rheumatic fever but knew of rheumatic heart disease since the age of 12 years. She had an appendectomy at 18, a successful caesarean section for her only pregnancy at 35, and a partial hysterectomy at 42.

Although she was under the care of a physician for the last 10 years of her life, during which time her physical activity was limited, nevertheless she had no symptoms other than mild dyspnea on effort until the last year. In the spring of 1952, at the age of 44, she complained of increasing dyspnea, ascribable in part to atrial fibrillation first noted then. Digitalis was begun and soon thereafter mercurial diuretics as well. Because her personality was characterized by extreme anxiety and emotional instability, hyperthyroidism as a complicating

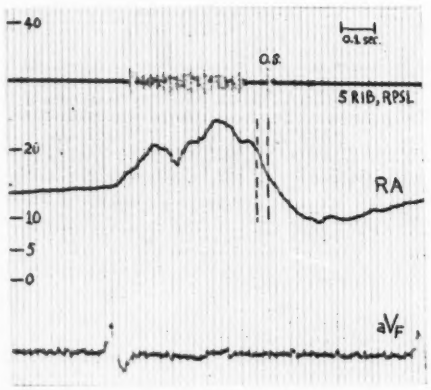

FIG. 5. Case 1 (E. S.). Simultaneous electronic recording on April 7, 1954 of a stethogram, the right atrial pressure (RA), and a modified lead aV_F (aV_F). In making the stethogram a bell 5 cm. in diameter was used on the fifth rib in the right parasternal line, and the sound filtered with a band pass of 400 to 800 cycles per second before being linearly recorded. The calibrations for the pressure curve in millimeters of mercury are shown on the left. The mean pressure was approximately 19 mm. Hg. The electrocardiogram is distorted by somatic tremors. Time lines, 0.02 sec.

The opening snap (O.S.) occurs 0.03 second after the onset of the steepest part of the slope of the atrial pressure pulse (interval indicated by dashed vertical lines), and approximately 0.05 second after the very beginning of this slope.

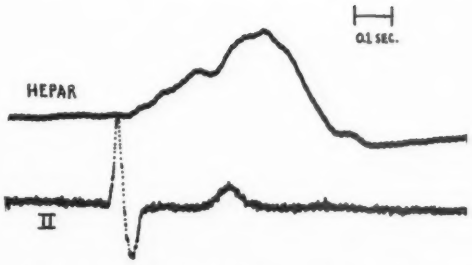

FIG. 6. Case 1 (E. S.). Hepatogram recorded by means of a piezo-electric crystal pick-up on the abdominal wall over the liver and a cathode ray oscillograph. The simultaneous record is electrocardiographic lead II. Similarity of the hepatic pulse to the right atrial pressure pulse (fig. 5, RA) and the jugular phlebogram (fig. 4) is to be noted. All show a prominent systolic "regurgitant" wave.

etiology was considered as a possibility. Several studies of the basal metabolic rate and determination of the radioactive iodine uptake failed to substantiate the suspicion.

She was admitted to Lenox Hill Hospital on May 18, 1953 for a period of two weeks; again on July 1, 1953 for a period of five weeks; transferred to the Psychiatric Hospital at Bellevue Hospital on August 7, 1953; and died there on August 11, 1953. These hospitalizations were really for a continuing and rapidly progressive illness.

When first admitted to the hospital the ventricular rate was 144, there was hepatosplenomegaly, the venous pressure was 250 mm. water, and the Decholin and ether circulation times were 50 seconds and 18 seconds, respectively. The venous pressure fell to 160 mm. water in five days after 1.5 mg of Gitaligen daily. She lost 5 pounds in weight with the aid of mercurials, after which she was discharged to her home with instructions to continue digitalis.

She returned one month later with pain in the right lower chest and right shoulder, hemoptysis, fever, nausea, extreme apprehension and further loss of weight. Examination revealed effusion in the right base and presumptive roentgenographic evidence of infarction in the right lower lobe. Edema occurred when an attempt was made to mobilize the patient. She eventually became hysterical and noisy to a degree which required transfer to a psychiatric hospital. There her condition remained essentially unchanged until a few hours before death when a shock-like state developed.

The *physical findings* differed only slightly from time to time. The patient was always loquacious, dyspneic, apprehensive, and showed variable degrees of hepatosplenomegaly, venous congestion, and in the last few weeks of life, pendent edema and right pleural effusion.

Except for the rate, the findings in the heart were quite constant. The point of maximum impulse was initially in the fifth intercostal space in the midclavicular line, later in the sixth intercostal space beyond this line. There was no thrill. The first sound at the apex was valvular; at the base, largely obscured by murmurs. At the apex there was a loud, long blowing systolic murmur. There was also a short, loud, rumbling diastolic murmur in the same area. At the base, but loudest in the aortic area, was a long, harsh systolic murmur. It was followed by a short, soft diastolic blow transmitted downward and to the left toward the apex. At the xiphisternum and in a circular area several centimeters in diameter below it (figure 1, E. C.) there was a high pitched, short, loud, diastolic snapping sound. This occurred just after the second sound which in this area was of greatly diminished intensity. A systolic murmur but no distinctive diastolic murmur could be heard in this area although one was recorded (figure 7). The ventricular rate varied from 144 to 80 at various times, and was always irregular. The blood pressure was usually in the range of 130 mm. Hg systolic and 85 diastolic.

Roentgenograms made on the initial admission (figure 8) disclosed a greatly enlarged heart involv-

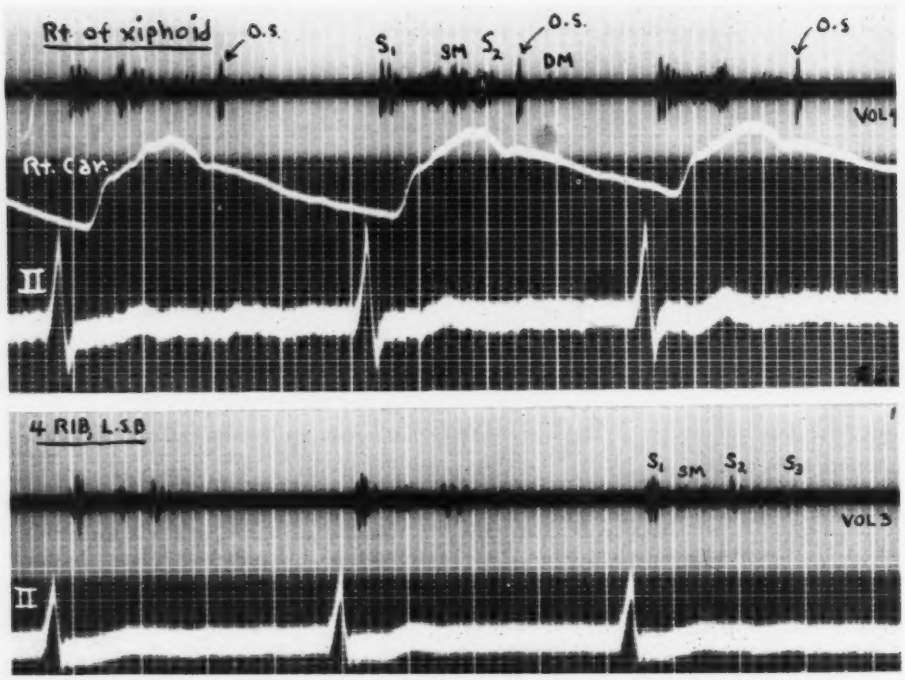

FIG. 7. Case 2 (E. C.). Stethograms made with a microphone to the right of the xiphoid on May 26, 1953 (upper record), and at the fourth rib at the left sternal border on July 14, 1953 (lower record). The records simultaneously made with the former are the right carotid arteriogram (Rt. Car) and lead II; with the latter a somewhat changed lead II. Instrumentation, symbols, and time lines as for figure 4.

The presence of the snap (O.S.) at the xiphoid, its absence at the left sternal border, but the presence of a later, low pitched, third sound (S_3) in the latter area are to be noted.

ing all chambers. Prominent features were the elongated right atrial border, and the obliteration of the cardiovascular angle. An esophagram (figure 8) disclosed considerable posterior displacement of the esophagus by an enlarged left atrium. The same view (right anterior oblique) showed a prominent right ventricular conus and pulmonary stem anteriorly and superiorly. The cardiac silhouette did not vary on subsequent examinations.

Electrocardiograms repeated at weekly intervals did not differ greatly one from the other (figure 9). All displayed atrial fibrillation, left deviation of the electrical axis of QRS, and depression of the S-T junction with inversion of the T waves in leads I, aV_L and V_5. Intrinsicoid (RS) deflections in leads from either side of the precordium were not delayed in onset. Some later records disclosed ventricular premature systoles, and on one occasion coupling ascribed to excessive digitalis.

Stethograms were recorded on several occasions, two of these being shown in figures 7 and 10. In figure 7 the upper record was made simultaneously with the right carotid sphygmogram and electrocardiographic lead II on May 26, 1953 when the microphone with a shallow bell 5 cm. in diameter was placed to the right of the xiphoid. In addition to an opening snap in this region (O.S.), the stethogram shows systolic (SM) and early diastolic (DM) murmurs. The second heart sound (S_2) shows poor definition. It was difficult to hear, and one observer apparently mistook the opening snap for the second sound in the area of the xiphisternum. The carotid sphygmogram, with a latency of 0.06 to 0.08 second due to inertia of the mechanical recording system, identified the opening snap as occurring well after the incisura.

The lower stethogram in figure 7 was made sometime later, on July 14, 1953, simultaneously with lead II, with the microphone at the fourth rib and left sternal border, the usual site of greatest audibility of the opening snap of the mitral valve. None could be heard in the area, and none was recorded. However, the record does show a low frequency (approximately 30 cycles per second) vibration (S_3) of approximately 1.5 cycles in length occurring 0.16 to 0.17 second after the beginning

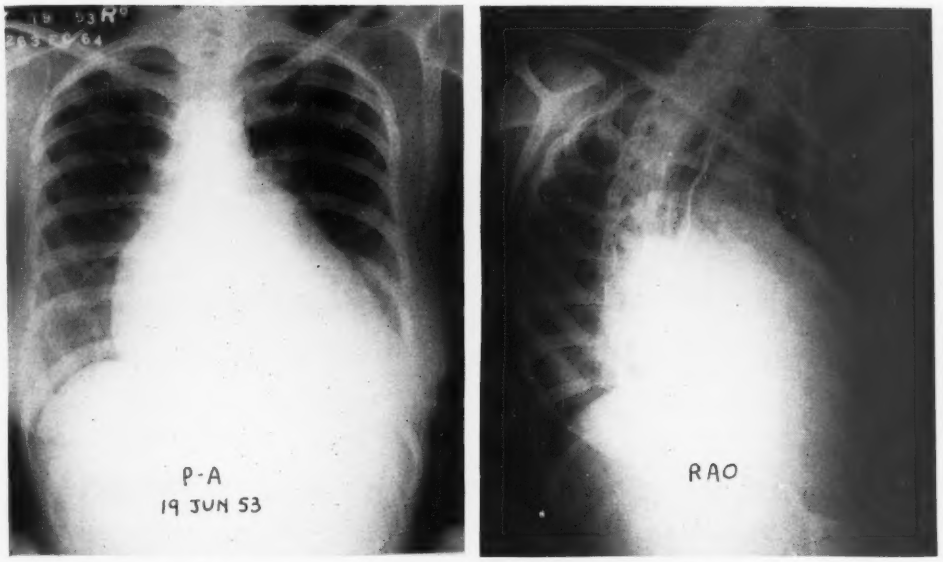

FIG. 8. Case (E. C.). Posteroanterior (P-A) and right anterior oblique (RAO) teleroentgenograms made on June 19, 1953. The barium filled esophagus of the latter (barely visible) is displaced backward. The right atrial curvature is not as prominent as in case 1 (fig. 2), and the left ventricle more so.

of the second sound. This could be heard close to the lower sternum. It was neither heard nor recorded elsewhere. It is believed to be a physical sign to which infrequent reference is made,[16] namely gallop rhythm limited to the right ventricle.

On the same day that this latter stethogram was made, three additional ones were recorded from the xiphoid with another instrument* (figure 10) both by stethographic and logarithmic recording at the same gain (upper records) and by stethographic recording at higher gain (lower record). Logarithmic recording did not alter the high frequency snap (O.S.) very much, while high gain recording greatly exaggerated its single, high frequency component.

The interval between the beginning of the second sound and the beginning of the opening snap was correlated with the length of the preceding cardiac cycle on several records. On one of these there was a direct relationship between the two (figure 11) as in the case of the opening snap of the mitral valve.[9, 18] Breath holding, required when recording heart sounds, apparently had no bearing on this relationship (figure 11). In another record, made at the same sitting but after the patient had been "resting" for a time, the average interval was fairly constant (0.084 to 0.097, mean of 0.092 second), and did not vary in any recognizable manner with the preceding cycle length. The word "resting" is placed in quotes because during the entire time of recording the patient was apprehensive and complaining. The fact that the second sound-opening snap interval became shorter (mean of 0.092 second compared with mean of 0.100 of values plotted in figure 11) and relatively fixed may mean that venous pressure toward the end of the recording was rising

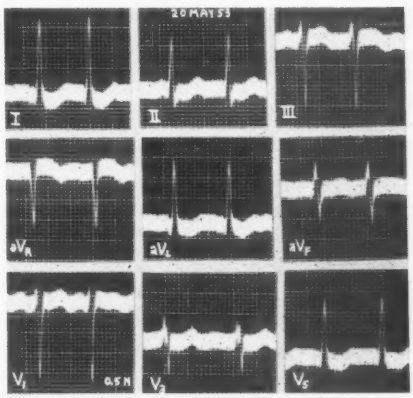

FIG. 9. Case 2 (E. C.). Electrocardiogram recorded on May 20, 1953. Symbols have the usual meaning[20]. The precordial leads V_1, V_3, and V_5 were made with sensitivity of the galvanometer half of normal (1 mv = 0.5 cm). Time lines, 0.04 second.

* Sanborn Instrument Company's Twin Beam Cardiette, Model 62.

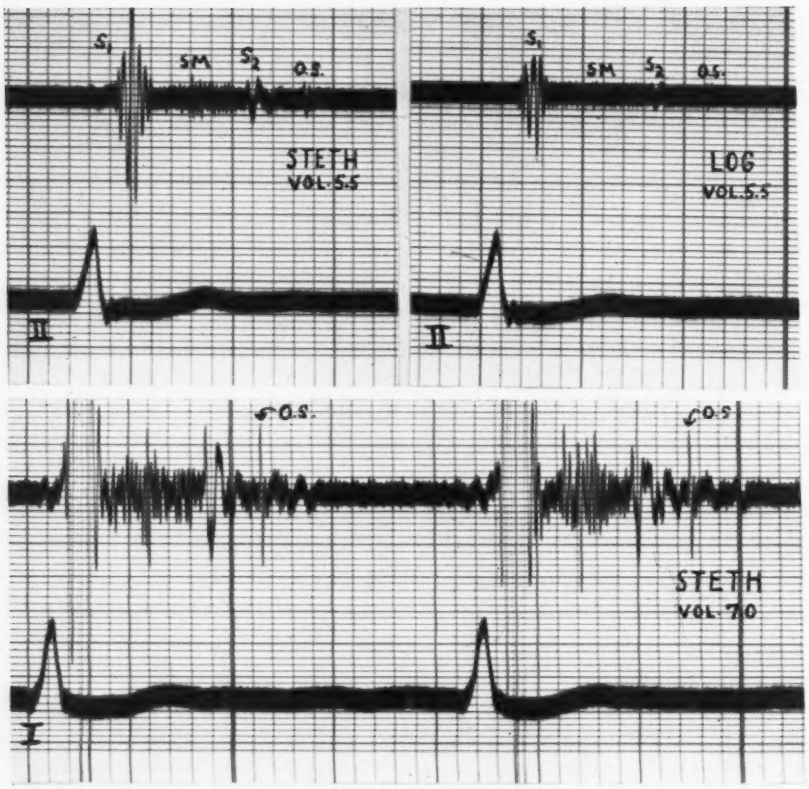

FIG. 10. Case 2 (E. C.). Additional stethograms made with another instrument (Sanborn Twin Beam) from the xiphoid simultaneously with lead II (II) or I (I). Recording was done stethographically (Steth.) and logarithmically (Log.)[13]. The latter had little effect on the opening snap of the tricuspid valve (O.S.) as recorded by the former. The lowest record shows a stethographic recording at high gain (vol. 7.0) which tends to bring out a single large vibration of the snap (O.S.). Time lines, 0.04 second.

and the gradient of pressure across the tricuspid valve was very high regardless of length of preceding cycle.[19] On all of the records of this patient the 2-O.S. interval had a mean value of 0.097 second, and a range of 0.068 second to 0.120 second (25 cycles measured).

Diagnosis. On the basis of the clinical and graphic data, the patient was regarded as having rheumatic heart disease with enlarged heart, mitral stenosis, mitral insufficiency, tricuspid stenosis, tricuspid insufficiency, aortic insufficiency, intracardiac thrombi, atrial fibrillation with ventricular premature systoles, and congestive heart failure. Pulmonary infarction was a complication. Although laboratory evidence was lacking, the fairly rapid course suggested possible activity of the rheumatic process in the myocardium.

Necropsy. Heart:*—The enlarged heart weighed 550 Gm. All chambers except the right ventricle were dilated. The dilated right auricle (appendage) disclosed some punctate hemorrhages and fibrinous exudate externally, a recent organizing thrombus, 3 cm. by 4 cm., internally. The right atrium showed a fine Chiari's network near the ostium of the coronary sinus. Both ventricles were hypertrophied (thickness of right 0.5 cm., of left 1.5 cm.). The patent coronary arteries showed only minimal lipid deposits.

The tricuspid valve was moderately stenotic, admitting only the tip of the index finger. The leaf-

* Necropsy was performed two hours post mortem by Drs. Irene Gleason, Resident Pathologist, and Cyril Solomon, Assistant Pathologist, Bellevue Hospital, New York.

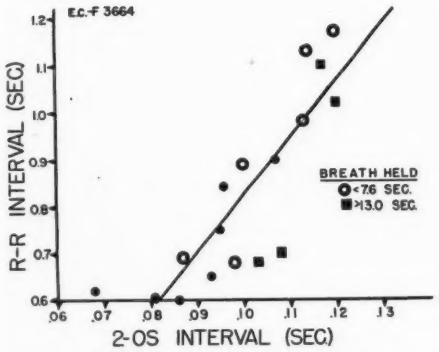

FIG. 11. Case 2 (E. C.). A graph to show the direct, linear relationship between the length of the preceding cycle (R-R interval) and the interval between the beginning of the second heart sound and the opening snap of the tricuspid valve (2-O.S. interval) in one record made on May 23, 1953. In order to demonstrate that holding the breath, as is required when making stethograms, had little effect on the relationship, the values obtained when the breath had been held for less than 7.6 seconds and the values obtained when the breath had been held more than 13.0 seconds are shown in open circles and squares, respectively. Intermediate times are shown as solid circles. The regression line was calculated ($y = 12.13, x - 0.389$). The overall mean for all plotted values of 2-OS interval is 0.100 second.

lets were scarred, contracted, fused, and the free margins were rolled. The chordae tendineae were also moderately thickened and shortened. The circumference of the closing margin was 6.5 cm. The pulmonic valve was normal. The mitral valve displayed a "fish-mouth" deformity with a stenotic orifice which just admitted the tip of an index finger. The leaflets were fused, rigid, thickened and calcified, and the line of closure was retracted upward. The attached chordae were moderately thickened and slightly shortened. The circumference of the orifice at the line of closure was 6.5 cm.

The aortic valve was stenotic to a degree which admitted a probe of only 1 cm. in diameter. The leaflets were thick and calcified and there were calcific excrescences not only on the ventricular aspects but also on the walls of the sinuses of Valsalva. Two cm. below one cusp there was a longitudinal raised area of the endocardium on the interventricular septum which measured 1 cm. by 0.3 cm.

Blood Vessels:—There was mild atherosclerosis of the aorta, most marked in the arch. The large pulmonary arteries displayed slight to moderate amounts of intimal atheroma and the smaller arteries disclosed distinct intimal thickening. The superior vena cava, the right and left innominate veins, the right and left subclavian veins, and the internal jugular veins were occluded by a fresh thrombus. Parts of this in the superior vena cava were organizing.

Other Findings:—In addition to bilateral pleural effusion (right 1.0 liter, left 0.3 liter), the somewhat smaller than normal though congested lungs revealed an organizing infarct in the right lower lobe of 5.0 cm. in diameter. Small branches of the pulmonary artery leading to the area were occluded by organizing thrombi. Microscopic sections showed irregular thickening and fibrosis of the alveolar walls in general. The liver was normal in size (1350 Gm.) and revealed only congestion. The right kidney showed an old infarct at its inferior pole which measured 1 cm. in diameter. The spleen and pancreas were congested. There was no microscopic evidence of active rheumatic infection in the heart.

DISCUSSION

The data presented in these two patients favor the belief that the diseased tricuspid valve, and especially the stenotic valve, is capable of making a sound on opening. This sound has been designated as the opening snap of the tricuspid valve.[10]

It is heard best in the "tricuspid area" but allowances must be made for displacements of this auscultatory area principally to the right and downward produced by hypertrophy and dilatation of the right sided chambers of the heart secondary in part to the usually associated mitral disease. Its duration is brief (approximately 0.02 second), and its intensity greater than that of the second sound occurring in the same area. In one patient (case 1) the intensity of the highest vibration had a value of approximately 86 decibels above the average threshold of hearing. No analysis of frequencies was made but some appeared to be in excess of 400 cycles per second, and the sound was distinctly high pitched and snapping. On the average (in both patients) it occurred 0.10 second after the beginning of the second sound. This interval was longer the longer the preceding cycle length but the correlation, with one exception (figure 11), was not definite. In the one case in which the measurement was made, the sound occurred not at the beginning but 0.05 second after the beginning of the rapid fall in atrial pressure as

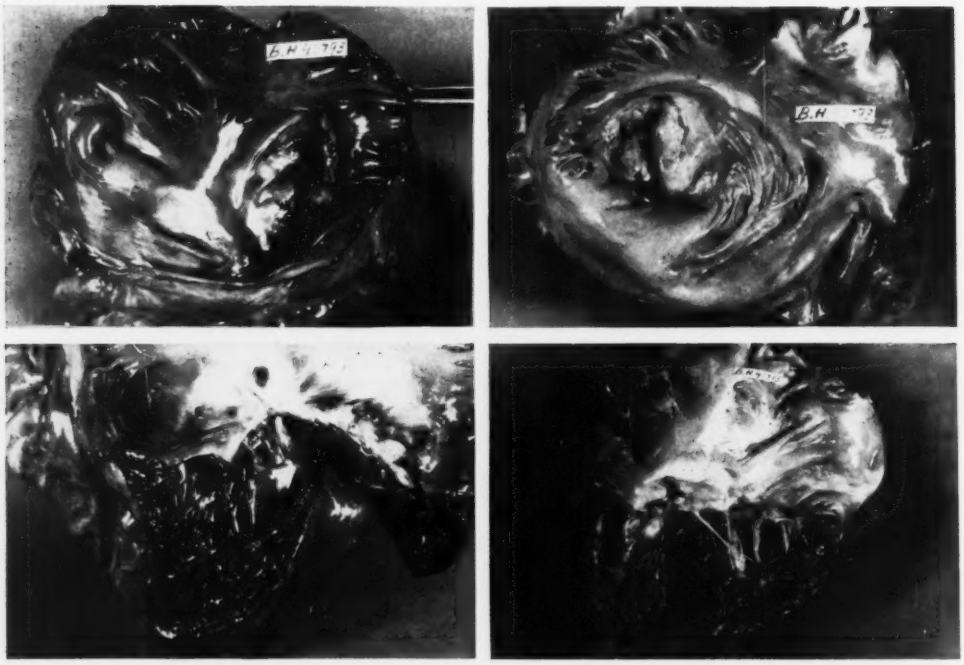

FIG. 12. Case 2 (E. C.). Two views of the stenotic tricuspid and mitral valves. *Above left*, the tricuspid valve viewed from the right atrium; *below left*, the incised tricuspid valve viewed from the right, with the right ventricle below, and the right atrium above. *Above right*, the mitral valve viewed from the left atrium; and *below right*, the incised valve viewed from the left with the left atrium above and the left ventricle below.

The orifice in each case admitted the tip of the index finger, but the mitral valve was rigid and calcified and incapable of independent movement. The stenotic tricuspid leaflets, though thickened, were pliable and movable. The dark material at the apex of the right ventricle and in the right atrium is postmortem clot (The photographs were made by Dr. Cyril Solomon).

measured on the right atrial pressure pulse. Much speculation on the reason can be made, including the possibility that the sound in this one case (E. S.) was not due to opening of the tricuspid valve. Its resemblance in timing and other characteristics, however, to the similar sound encountered in the other case (E. C.) with proven tricuspid stenosis makes some other explanation likely. Clearly an insufficient and stenotic tricuspid valve will remain open during isometric relaxation of the right ventricle. It is likely that atrial pressure, under these circumstances, will fall at the beginning of isometric ventricular relaxation. Flow, on the other hand, ordinarily signalled in venous sphygmograms by the peak of the v wave, probably cannot become maximal until isometric relaxation of the ventricles terminates. Only simultaneous records of pressures in the right atrium and right ventricle could give irrefutable evidence on the significance of a gradient in pressure between the two chambers in the creation of the tricuspid snap.

The right ventricular pressure was not recorded in case 1 and therefore a gradient in pressure between the right atrial mean pressure or Z-point pressure and the end diastolic right ventricular pressure as shown by Ferrer and her associates[17] in tricuspid stenosis could not be demonstrated. However, the mean pressure in the right atrium was unusually high (19 mm. Hg) and the possibility that the gradient under consideration existed is good. The fact that clinically and hemodynamically

the patient displayed dominantly insufficiency rather than stenosis of the valve does not militate against the diagnosis of the latter defect.

The opening snap of the tricuspid valve must be differentiated from other sounds in early diastole. Usually no difficulty will be encountered by virtue of the relatively peripheral precordial area in which this sign is heard. In some patients with mitral stenosis, the opening snap of the mitral valve can be heard well to the right of the sternum and as low as the xiphoid cartilage but the intensity in these regions is less than at the lower left sternal border. Other sounds, usually of low pitch, have been heard in a few patients at or near the right lower border of the sternum and xiphisternum which may give difficulty but the mechanism of their creation was not apparent. The observations accentuate the need for further auscultatory scrutiny of the region in patients with heart disease.

The data are too meager and the dynamics too complicated by associated valvular and myocardial lesions to attempt an assessment of the degree of stenosis of the tricuspid valve from the phonocardiogram such as has been done by Wells in cases of mitral stenosis.[19]

Summary

A short, loud, snapping sound early in diastole was heard and recorded near the xiphisternum in two patients with rheumatic heart disease. The sound was similar in almost all respects to the opening snap of the mitral valve except for its area of audibility. In one of the patients the presence of tricuspid stenosis was demonstrated at necropsy; in the other there was convincing clinical and hemodynamic evidence, at least, of organic tricuspid valvular disease. This physical sign, the opening snap of the tricuspid valve, has practical diagnostic value.

Summario in Interlingua

In duo patientes con morbo rheumatic del corde, un clac esseva audite al xiphisterno o infra e al dextere de illo. Iste clac esseva breve, forte, e alte e occurreva al comenciamento del diastole. A parte le differente area de su audibilitate, le clac resimilava in le auscultation le clac de apertura del valvula mitral. Ambe patientes exhibiva signos physic de morbo del valvulas tricuspide e etiam mitral e aortic. In un del casos le datos hemodynamic indicava morbo tricuspide. In le altere caso stenosis tricuspide esseva constatate necropticamente. Le clac esseva un sono anormal que esseva considerate como producite per le apertura del valvula tricuspide.

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A Critical Evaluation of the Roentgen Criteria of Right Ventricular Enlargement

By MARCY L. SUSSMAN, M.D. AND GEORGE JACOBSON, M.D.

We believe that right ventricular enlargement is "over-diagnosed" radiologically, and this becomes apparent when radiologic interpretation is attempted without the help of other data. We tested this impression in a study of 25 cases of tetralogy of Fallot and 40 cases of other types of congenital pulmonary stenosis. In these cases there was usually no right ventricular dilatation. The roentgen determination of right ventricular hypertrophy was found to be decidedly of limited value. There were few infants in the present study and the conclusion should not be construed as necessarily including this group.

THE commonly accepted roentgen criteria of right ventricular enlargement are: 1. Enlargement of the outflow tract anteriorly with bulging into the lung-filled triangle of the anterior mediastinum, seen earliest in the right anterior oblique position. 2. Enlargement in the posteroanterior position usually upward and to the left, resulting in filling of the concavity in the left border between the knob of the aorta and the left ventricle. 3. In the left anterior oblique position, anteriorly, there is a bulge of the lower portion of the contour. An angulation may be observed at the upper end of this bulge. The diaphragmatic portion of the heart increases in length with displacement of the interventricular groove posteriorly, then upwards, on the lower contour.[1]

These criteria have, in general, been derived from postmortem comparisons and, in addition, such animal experiments as those of Nemet who applied metallic markers to the interventricular septum. Since the advent of angiocardiography, doubt has been cast on these criteria. Thus it has been pointed out that, in the left oblique position, it is the right atrium that presents on the right contour in most cases and not the right ventricle; furthermore that the indentation seen radiologically in the left oblique position and called the interventricular groove does not regularly correspond to the position of the interventricular septum.[2] Moreover, in the posteroanterior view, the pulmonary conus (defined as the subvalvular portion of the right ventricle) does not ordinarily approach the left contour. Early observers such as Assmann recognized this from anatomic studies. In the right oblique position, the differentiation of pulmonary conus and artery is difficult; the precise limits of the conus inferiorly are even more difficult to establish.

We have felt, therefore, that the conventional criteria of right ventricular enlargement measure, most often, changes in the right atrium and pulmonary artery, either primary or the result of displacement. Only infrequently is a direct evaluation of the ventricle itself possible. Furthermore the range of "normal" variation is considerable. It is anticipated, therefore, that moderate hypertrophy of the right ventricle without dilatation will not be recognized under ordinary circumstances and this is substantiated also by the paucity of radiographic confirmation in most cases of cor pulmonale.[3]

It has been our impression also that right ventricular pressure and chamber size are essentially independent functions even though we recognize that increased diastolic volume is associated with some pressure increase. While right ventricular hypertension is commonly present in many congenital cardiac lesions where there is no increase in pulmonary flow, right ventricular dilatation is infrequent until the advent of failure in those who survive beyond infancy. We believe that right ventricular enlargement is "overdiagnosed" radiologically, and this becomes apparent when radiological interpretation is attempted without any other data. To test these impressions we

GROUP 1. *"Pure" Pulmonary Stenosis. Arterial Blood Saturation 90% or Greater*

Case No.	Case	Age	Ecg.	X-ray				Angiocardiogram	Pressures		Operation
				Overall size	R.O.	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm. Hg	R.V. $\frac{s}{d}$ mm. Hg	
1	W. M.	7	R.V.H. Incomplete R.B.B.B.	1*	0	2	3		25/12	100/10	Little resistance at valve. Post stenotic dilatation.
				2*	0	0–1	3				
2	R. O.	26	R.V.H.	0	0	1	3	None.	15/5	70/8	None.
				0	0	0	2	Normal heart. Pulm. art. 3			
3	R. G.	9	R.V.H.	0	0	0	3	Normal heart. Pulmonary artery 3.	30/20	70-115/0-5	
				0	0	0	0–1	Normal heart. Pulmonary artery 2.			
4	H. M.	13	R.V.H.	1	1	1	1	Normal heart. Pulmonary artery 2.	13/6	37/6	None.
				1	1	0	0	Normal heart. Normal artery.			
5	P. S.	12	R.V.H.	0	0	0–1	2	None	10/4	116/8	None.
				0	0	0	0	0			
6	V. L.	14	R.V.H.	0	0	0	3	Normal heart. Pulmonary artery 2.		67-87/5	None.
				0	0	0	1	Normal heart. Pulmonary artery 1.			
7	E. C.	12	R.V.H. Prolonged A.-V. conduction.	0	0	2	3	None.	15/10	50/0	Marked resistance. Marked post stenotic dilatation.
				0	0	0	2				
8	E. A.	21	R.V.H.	2	0	2	2	R.A. & R.V.3. Pulmonary artery 2.	15-25/10	115-145/3-8	Moderate resistance. Marked post-stenotic dilatation.
				0–1	0	0	1	R.A. 1. Pulmonary artery 1.			

* Degree of enlargement graded 0–3. The two lines of figures are the values assigned independently by the two authors.

reviewed the available clinical, radiographic, angiocardiographic and catheterization data in 40 cases of congenital pulmonary stenosis and 25 cases of the tetralogy of Fallot. We chose these conditions for the study of the problem because right ventricular hypertrophy and/or dilatation is a striking component and because complete data were more likely to be available in cases of these conditions. We applied the conventional radiographic criteria of right ventricular enlargement. We must emphasize however that most of our subjects were no

GROUP 2. *Pulmonary Stenosis. Arterial Blood Saturation Less Than 90 Per Cent*

Case No.	Case	Age	Ecg.	X-ray				Angiocardiogram	Pressures		Arterial Saturation	Operation
				Overall size	R.O.	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm.Hg	R.V. $\frac{s}{d}$ mm. Hg		
	R. W.	6	R.V.H.	3	3	2	2		30	180	89	Valvulotomy
				2	2	1	0		15	15		
11	G. T.	3½	R.V.H.	1	0	2	1		30	50	88	None. Catheterization
			probable	0	0	0	0		20	8		suggests transposed vein.
1	M. M.	10	R.V.H.	1	0	2	2	R.V. 2+.			87	Valvular stenosis.
								P.A. 1+	20	100		
				0	0	0	2	normal	6	5		
12	C. F.	4	abn.	0	0	2	2		25	30-37	83	None.
			R.V.H.	0	0	0	1		14	0-5		
13	M. N.	4	R.V.H.	2	0	2	0		22	85	78	Distinct resistance. Moderate post-stenotic dilatation.
				0	0	0	0		10	10		
14	Q. P.	19	R.V.H.	0	0	1	3	R.A. 1			87	Little resistance.
								P.A. 3	16	80-88		
				0	0	0	3	Normal	8	4		
								P.A. 0–1				
15	D. R.	30	R.V.H.	0	0	2	3		16	110-120	85	Marked stenosis.
				0	0	0	3		4	0-5		
16	M. L.	6	R.V.H.	2	2	2	0	R.V. 3.			82	Valvular stenosis.
								P.A. 1	22	95-100		
				0–1	1	1	0	R.V. 0–1	12	3-10		
								P.A. 1–2				
17	R. A.	6	R.V.H.	0	0	1	0	Normal	27	60	85	Valvulotomy.
				0	0	0	0		16	0		
18	R. R.	14	R.V.H.	0	0	0–1	3		35	125	85	None.
				0	0	0	3		15	25		
19	D. G.	20	Normal	0	0	0	3		20	40	89	None.
				0	0	0	2		10	15		

infants, and our conclusions do not necessarily apply to the latter class of patient.

PROCEDURE

The roentgenograms of all cases of pulmonary stenosis were reviewed by both authors independently, without reference to the clinical data. We used no actual measurements. In about one-half, we repeated the review after having seen the films together and redefined our criteria. In many, perhaps most, cases, we found that we did not make precisely the same interpretation. Our joint session demonstrated that this discrepancy was partly a matter of semantics; one of us might describe a three-plus enlargement, where the other called it two-plus. However, even in final independent reviews, there was not complete concurrence either with each other or with ourselves. The results are listed in the tables in separate horizontal columns. This is consistent with other multiple reading tests. Overall size was judged in the posteroanterior view; impressions of right ventricular enlargement and pulmonary size were judged in left and right oblique views, and graded on a 0 to 3 scale.

We found a similar discrepancy in the interpretation of the angiocardiograms but this was not surprising since there is little material in the literature

GROUP 3. *Pulmonary Stenosis With Demonstrated Intracardiac Shunt*

Case No.	Case	Age	Ecg.	X-ray				Angio-cardiogram	Pressures		Arterial Saturation	Shunt	Operation
				Over-all size	R.O	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm. Hg	R.V. $\frac{s}{d}$ mm. Hg			
20	T. R.	28	R.V.H.	2 2	2 2	0 0	2 1	None	27/16	60/0	90	I.A.	None.
21	R. G.	11	R.V.H.	1 1	0 0	0 0	2 1	R.V. 1+ P.A. 2+	20/10	104/2	93	I.V.	None.
22	R. L.	26	R.V.H.	0 1	— —	0 0	0 0		15/3	50/0	86	I.V.	None.
23	T. D.	7	R.V.H.	0 2	0 1	0 1	1 2		20/10	60/5	95	T.V. I.V.	None.
24	L. V.	16	? Normal	0 1	0 0	0 0	1 1		24/8	46/7	96	I.A. ??I.V.	None.
25	R. M.	14	None rec'd.	0 0	0 0	0 0	2 1		20/10	42/8	91	I.V. L.A.	None.
26	J. M.	5	R.V.H.	0 1	1 1	1 1	1 1		17/10	28/2	92	I.A. or T.V.	None.
27	R. W.	18	Normal	0 0	0 0	1 1	3 2		15/10	35/5	86	I.V.	None.
28	B. H.	23	R.V.H.	0 0	0 0	0 0	0 1		5	50	69	I.A.	None.
29	G. A.	17	R.V.H.	0 0	1 0	0 0	0 0		12/0	150/0	Prob. low	I.A. or T.V.	Blalock
30	M. S.	2½	? R.V.H.	0 0	0 0	0 0	0 0		16/10	45/5	88	? ductus	None.
31	S. M.	13	? R.V.H.	1 2	0 2	2 1	2 1		18/12	65/0	95	I.V. I.A. or T.V.	None.
32	J. M.	23	R.V.H.	0 1	— —	— —	0 0		18/3	45/8	86	I.A.	None.
33	L. M.	12		0 0	0 0	0 0	0 0		19/8	63/5	88	T.V.	Valvulotomy. Marked stenosis.
34	R. C.	3	R.V.H.	1 1	0 1	0 0	1 1		25/10	40-48/0-5	86	I.V.	None.
35	L. M.	31	combd. heart strain	3 3	3 2	3 2	1 1		25	61	85	I.V. A.I. & A.S. clinical.	None.
36	J. D.	4		0 1	1 1	1 1	0 0		15/10	32/2	84	I.V. ? I.A.	None.

GROUP 3.—*Cont.*

Case No.	Case	Age	Ecg.	X-ray				Angiocardiogram	Pressures		Arterial Saturation	Shunt	Operation
				Overall Size	R.O.	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm. Hg	R.V. $\frac{s}{d}$ mm. Hg			
3	J. C.	28	R.V.H.	1 2	0 1	3 2	0 0		$\frac{27}{10}$	$\frac{90}{10}$	91	I.A. ? T.V.	None.
3	J. M.	7	R.V.H.	0 0	0 0	0 0	0 0		$\frac{25}{7}$	$\frac{88\text{-}40}{5\text{-}10}$	100	I.V. Over-riding aorta	Valvulotomy. Little resistance
3	A. N.	3	R.V.H.	3 3	— —	— —	0 0		$\frac{14}{10}$	$\frac{85}{15}$	80	I.A. or T.V.	Valvulotomy. Slight resistance.
4	D. K.	13	R.V.H.	1 2	0 0	0 0	0 0		$\frac{28}{5}$	$\frac{105\text{-}120}{15\text{-}10}$	90	I.V. Over-riding aorta	Valvulotomy. No definite obstruction.
41	R. L.	16	R.V.H.	0 1	2 1	0 1	1 1		$\frac{20}{7}$	$\frac{35}{5}$		I.A. or T.V.	None.
42	A. A.			0 0	1 1	0 0	2 0		$\frac{20}{8}$	$\frac{50\text{-}70}{0}$		I.A.	None.

which quantitates the average size of the chambers and the range of normal variation. Interpretation is largely a matter of personal evaluation. The electrocardiographic interpretations recorded on the patients' charts were accepted. Pressures and oxygen determinations were those made during routine catheterizations.

RESULTS

Group 1. This group consisted of eight cases of what we thought to be isolated or "pure" pulmonary stenosis. The diagnosis was based on the presence of right ventricular hypertension with a marked drop in pressure in the pulmonary artery as compared with the ventricle. In none did the catheter pass through any abnormal channel. The arterial blood oxygen saturation was 90 per cent or greater (90 per cent was chosen arbitrarily to indicate that unsaturation was not present or was insignificant). In five cases, we agreed that the heart was normal in overall size. In three cases we agreed there was enlargement but we differed as to the degree. We agreed that the right oblique position gave no additional information in these cases. Our greatest disagreement was in regard to the interpretation of the left oblique position where one of us felt that there was no deviation from average in any of the cases, while the other felt that a "shelf" might be present in five cases and was definitely present in two. We were surprised to find that we did not always agree on whether we thought the pulmonary artery was dilated from conventional films. In this group, our disagreement in the interpretations of the angiocardiograms was insignificant. In only one case, E. A. (case 8) was there disagreement regarding the degree of enlargement of the cardiac chambers and the pulmonary artery.

There was no correlation between the right ventricular pressure and the size of the heart and its individual chambers. Thus R. G. (case 3) with a right ventricular pressure of 70–115/0–5, had a normal sized heart and normal angiocardiogram aside from dilated pulmonary artery. P. S. (case 5) presented similar findings. Yet E. C. (case 7), with a pressure of 50/0 in the right ventricle, was interpreted by one of us as showing a two-plus enlargement of the right heart in the left oblique position. There was no correlation between the size of the pulmonary artery and the pressure in it, or the pressure gradient between it and the right ventricle, although in a general

GROUP 4. *Tetralogy of Fallot*

Case No.	Case	Age	Ecg.	X-ray				Angiocardiogram	Pressures		Arterial Saturation	Operation
				Overall size	R.O.	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm.Hg	R.V. $\frac{s}{d}$ mm.Hg		
43	A. N.	17	R.V.H.	0 0	0 0	0 0	0 0	Normal chambers. P.A. normal (0) Dye into aorta.	$\frac{11}{7}$	$\frac{115}{5}$	73.8	P.A. sma[illegible] under creased pres Patent du[illegible]tus.
44	D. C.	32	R.V.H.	0 0	1 0	0 0	−1 −2	R.A. 2 (0) P.A. −2.	$\frac{25}{20}$	$\frac{75}{5}$	44	Blalock. P[illegible]A. fair Decreased pre Catheteri[illegible]tion suggested single tricle.
45	J. S.	3	R.V.H.	2 2	2 2	2 3	0 0	R.A. 2 (0) R.V. 1 (0) Dye into aorta.	$\frac{20}{10}$	$\frac{120}{10}$	44	Blalock.
46	S. S.	4		0–1 +1	2 0–1	1 1	−1 −1	R.A. 2 (2) Small P.A. (−1) I.A. defect. Overriding aorta.		$\frac{90}{5}$		PM. Pulm[illegible]nary s sis. Aort[illegible] over I.V.S. defe[illegible]ct: I.A fect not f[illegible]nctio
47	D. P.	2½	R.V.H.	0 0	0 0	0 0	−1 0–1		$\frac{20}{5}$	$\frac{85}{0}$	65	None.
48	R. S.	4	R.V.H.	2 2	— —	— —	−1 −1	R.A. 1 (1) R.V. 2 (1) P.A. 0–1 (−1) Small shunt.	$\frac{15}{8}$	$\frac{80}{5}$		Potts.
49	J. Q.	21	R.V.H.	0 0	0 0	0 0	0 0			$\frac{90}{0}$	75	Valvulotomy. markedly dil Shunt not proved.
50	J. G.	7	R.V.H.	0 0	1 0	0 0	1 0	R.A. 2 (1) R.V. 1 (1) P.A. 1 (0–1)		$\frac{100}{2}$		Valvulotomy. large reduced sure. I.A. defect pected. Not prove
51	D. N.	5	R.V.H.	2 1	2 1	0 0	0 −1	Rt. arch. I. V. defect	$\frac{25}{12}$	85	85	Blalock. Pulmo artery poor pulsat
52	C. G.	12	R.V.H.	0 0	2 1	0–1 0	3 2	Right arch	$\frac{18}{9}$	$\frac{42}{5}$	81	Blalock. P.A. feeble pulsations.
53	G. B.	21	R.A.D.	0 0	2 0	1 1	−1 −1	P.A. 0	$\frac{30}{20}$	$\frac{60}{30}$	72	
54	R. D.	25	R.V.H.	0 0	0–1 0	0–1 0–1	0 −1	R.A. 1 (1) R.V. 1 (0). ? Shunt to aorta. P.A. 0	$\frac{20}{8}$	$\frac{95}{8}$	82	Valvulotomy. S not proven.
55	D. M.	7	R.A.D.	3 2	0 0	2 2	−1 −1	None.		85	69	PM. Marke[illegible] infun ular steno[illegible]s. I defect. Ano[illegible]alous veins.

GROUP 4.—*Cont.*

Case No.	Case	Age	Ecg.	X-ray				Angiocardiogram	Pressures		Arterial Saturation	Operation
				Overall size	R.O.	L.O.	Pulmonary artery		P.A. $\frac{s}{d}$ mm.Hg	R.V. $\frac{s}{d}$ mm.Hg		
56	C. G.	19	R.V.H.	0 0	0 0	0 0	−1 −1					PM. Tetralogy.
57	J. C.	3	R.V.H.	0 0–1	— —	2 1	−1 −1	R.V. 3 (2) P.A. −1 (−1). Small shunt to aorta.	$\frac{26}{12}$	$\frac{70}{9}$		Blalock.
58	G. C.	5	R.V.H.	0 1	0 2	0 2	0–1 0–1			$\frac{75}{0}$		Blalock.
59	B. M.	27	R.V.H.	2 1	0 0	2 1	0 0		$\frac{30}{22}$	$\frac{130}{18}$		
60	C. R.	27	R.V.H.	3 2	3 2	3 2	0 −2		$\frac{10}{2}$	$\frac{80}{0}$	52	PM. P.S. IVSD. Patent foramen ovale.
61	S. D.	20		2 1	2 1	0 0	−1 0		$\frac{2}{10}$	$\frac{135}{-5}$	62	Blalock.
62	J. S.	3	R.V.H.	0 1	1 1	0 1	−1 0	R.A. −0 (1) R.V. 0–1 (0) P.A. 1				Blalock.
63	F. S.	30	R.V.H.	0 0	0 0	0–1 0	−1 0		10	$\frac{125}{5}$		None.
64	D. M.	38	R.V.H.	0 0	0 0	0 0	2 2	R.A. 0 (0) R.V. 0 (0) P.A. 2 (2)	$\frac{12}{17}$	$\frac{150}{5}$	83	None.
65	A. M.	4	R.V.H.	1 0	0 0	0 0	−1 0			$\frac{85}{5}$		Blalock.

way the greater the pressure gradient, the larger was the artery. However, the most significant observation is that marked right ventricular hypertension was present without detectable enlargement of the chamber, probably because there was hypertrophy without dilatation. The electrocardiogram was more consistent in that all cases were interpreted as indicating right ventricular hypertrophy.

We do not presume to evaluate critically the operative findings. Nevertheless it is worthy of note that, judging by the surgeons' notes, correlation was lacking also between the degree of resistance which was met at the pulmonary valve at valvulotomy and the pressure gradient.

Group 2. This group consisted of 11 cases in which the pressure gradient between the right ventricle and pulmonary artery suggested pulmonary stenosis. Eight were operated and confirmed. In this group the arterial blood oxygen saturation was less than 90 per cent which we assume probably indicates a right-to-left shunt, but there was no other confirmation. The lack of correlation between pressures and chamber size was again apparent in this group. In spite of disagreement between the authors in their estimation of right ventricular

enlargement, it is strikingly evident that marked right ventricular hypertension can be present in the presence of cardiac contours which we both agreed were within normal limits. If the more conservative judgment is accepted, there was only one case in this group with roentgen evidence of right ventricular enlargement.

Our disagreement extended to the interpretation of the angiocardiogram and even into our estimation of the size of the pulmonary artery. It is our feeling that the major difficulty in estimation of the latter is the varying location of the bifurcation of the pulmonary artery and the degree to which the left pulmonary artery is superimposed on the shadow of the main pulmonary artery.

We were surprised that these cases with more marked oxygen unsaturation of the arterial blood were not more consistently associated with demonstrable right ventricular enlargement. If this finding of unsaturation can be interpreted as indicating a right-to-left shunt, which is certainly not proven, it would be anticipated that the increased blood flow would tend to produce dilated chambers. It might be significant that the electrocardiogram did not as consistently suggest right ventricular hypertrophy in this group as in group 1. The three cases in which the evidence was equivocal or absent were those with lesser degrees of right ventricular hypertension.

Group 3. This group consisted of 23 cases of pulmonary stenosis in which catheterization data afforded definite evidence of an intracardiac shunt. We could not estimate the size of the shunt in a sufficient number of cases to justify including this data. Our agreement in the roentgen interpretation of this group was better, differences being largely in degree, with no consistent trend. For this reason it is even more striking that only in eight cases was there an increase in overall size. In only six cases did we feel that there was roentgen evidence of right ventricular enlargement. These were not consistently associated with marked right ventricular hypertension. Thus J. M. (case 32) and R. W. (case 27) showed systolic ventricular pressures less than 40 mm. Many of the cases presenting severe right ventricular hypertension, such as G. A. (case 29) and J. M. (case 32), showed no cardiac or chamber enlargement. It is curious that in this group also the resistance at the pulmonary valve encountered at valvulotomy seemed to bear little relation to the pressure gradient. Recently at a postmortem examination of one patient in this group (A. N., case 39), no evidence of pulmonary stenosis was found. It would appear from this case, and other experience, both personal and in the literature,[4] that a marked pressure gradient between right ventricle and pulmonary artery may occur without organic pulmonary stenosis. There is no entirely satisfactory explanation, but apparently it is related functionally to the presence of an intracardiac shunt and the dilated pulmonary artery.

Group 4 consisted of 25 cases of tetralogy of Fallot as the basic lesion. In some cases there were additional lesions which did not appear to significantly alter the dynamic pattern. In all cases in which an electrocardiogram was done (23), except one, there was the pattern of right ventricular hypertrophy. As in the other groups there was no consistent correlation between pressures and the apparent size of the right heart chambers and pulmonary artery, whether judged from the conventional films or the available angiocardiograms. In only eight was the heart enlarged as far as the transverse diameter was concerned. In seven the right heart was judged to be dilated in the left oblique position. In an additional three cases, the right oblique position suggested some right ventricular enlargement. In 15 cases, therefore, the authors agreed that there was no evidence of right ventricular enlargement. In all but two, the pulmonary artery was normal or less than normal in diameter. In two, one confirmed at operation and the other by angiocardiogram, the pulmonary artery was dilated.

Summary

1. The present report does not include a study of infants and the conclusions should not be construed as necessarily applying to them.

2. The cases reported here were diagnosed primarily by cardiac catheterization. The

finding of a systolic pressure gradient between the right ventricle and pulmonary artery does not necessarily establish the presence of an organic pulmonary stenosis. There is evidence that occasionally such a gradient may exist functionally in the presence of an intracardiac shunt.

3. In the majority of patients with pulmonary stenosis, with or without an intracardiac shunt, the right ventricle is not dilated as far as can be determined radiologically. The right ventricular hypertrophy which is present consistently cannot be demonstrated accurately by roentgenologic methods other than angiocardiography and is indicated better by electrocardiography.

4. The pressure in the right ventricle and its size are independent functions.

5. The roentgen evaluation of the size of the right ventricle is of limited value. It is subject to considerable variation between the evaluations of experienced examiners; indeed not infrequently, several evaluations of a single examiner differ.

6. Right ventricular enlargement, in our opinion, is "overdiagnosed" radiologically. The diagnosis is of independent value only when the demonstration is unequivocal and is made without psychological preparation by other clinical data.

7. The customary text-book dictum that the right ventricular change in certain congenital lesions can *usually* be demonstrated radiologically was not found to be true in our cases.

Summario in Interlingua

Iste studio non include infantes e su conclusiones non es necessarimente applicabile a illes.

Le casos hic reportate esseva diagnosticate primarimente per catheterisation cardiac. Le constatation de un gradiente de pression systolic inter le ventriculo dextere e le arteria pulmonar non demonstra necessarimente le presentia de un organic stenosis pulmonar. Il ha datos in supporto del conception que tal gradientes existe a vices functionalmente in le presentia de un derivation intracardiac.

In le majoritate del patientes con stenosis pulmonar—con o sin derivation intracardiac—le ventriculo dextere non es dilatate in tanto que es determinabile per medios radiologic. Le hypertrophia dexteroventricular que es presente sin exception non pote esser demonstrate exactemente per medios roentgenologic altere que angiocardiographic. Illo se manifesta plus clarmente in le electrocardiogramma.

Le pression in le ventriculo dextere e le dimensiones de illo es functiones independente.

Le evalutation roentgenologic del dimensiones del ventriculo dextere es de valor restringite. Iste evalutation varia considerabilemente ab un experto al altere. De facto, il non occurre infrequentemente que plure evalutationes per le mesme experto non es identic.

In nostre opinion, allargamento dexteroventricular es "super-diagnosticate" per le radiologos. Iste diagnose es de valor independente solo in casos de demonstration non-equivoc e quando illo es facite sin preparation psychologic per contacto con altere datos clinic.

In nostre casos nos non poteva confirmar le assertion frequentemente trovate in le manuales que in certe lesiones congenite le cambiamento dexteroventricular es *usualmente* demonstrabile per medios radiologic.

Acknowledgment

The authors are deeply grateful to Doctor George C. Griffith and his group at the University of Southern California School of Medicine, Department of Medicine (Cardiology) for the generous use of their records and unfailing critical advice.

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The Demonstration of Left Atrial Enlargement by Body Section Radiography

By BERNARD H. PASTOR, M.D., GEORGE T. WOHL, M.D. AND L. THEODORE LAWRENCE, M.D.

The enlarged left atrium may be poorly demonstrated in conventional roentgenograms. It can be delineated clearly in such cases by appropriate body section films. Body section radiography may also be helpful in the study of other ill-defined cardiac and vascular contours and in the demonstration of intracardiac calcification.

ALTHOUGH the signs of left atrial enlargement are well known, they are sometimes difficult to demonstrate in conventional roentgenograms. We have found body section radiography helpful in delineating enlarged left atria in patients in whom the enlargement was not satisfactorily defined by the standard roentgenologic method of heart study.

Body section radiography is a technic of comparatively recent development. Since Bocage first studied the method in 1917, numerous refinements and modifications have been introduced and have variously been called stratigraphy, planigraphy, tomography and laminography.[1, 2] The basic principle of all of these techniques is the same. Simultaneous parallel reciprocal movement of the x-ray tube and film casette about a fulcrum of adjustable height takes place during the exposure. Only one section of selected depth and predetermined thickness corresponding to the position of the fulcrum is continuously in focus. Details in this section alone are clear, other levels being blurred out in the process. The importance of such a technique has long been recognized in the study of lesions in the chest, where superimposition of tissues of different density may obscure underlying infiltrations or cavities. It has less frequently been applied to the study of laryngeal, bone or other lesions.

A recent report describes the use of planigraphy for the visualization of intracardiac calcification,[3] but the method has so far had little application in the study of the heart.

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All of our laminographs were made with a General Electric Ordograph. This is a hydraulicly driven mechanism with a tube travel of 15 inches, 40 inches above the table top. The average technical factors employed were 86 kilovolts, 50 milliamperes, 2½ seconds with Bucky technique. The desired levels were estimated by reference to a 6 foot, 14 x 17 inch chest film in each case and numerous cuts were made at 1 cm. intervals on 10 x 12 inch film. We have found that satisfactory films can almost always be obtained between 10 and 14 cm. from the table top, thereby permitting economy in the use of only four or five films.

Because the left atrium occupies a relatively concealed position behind the heart in the frontal projection, the recognition of left atrial enlargement in conventional roentgenograms

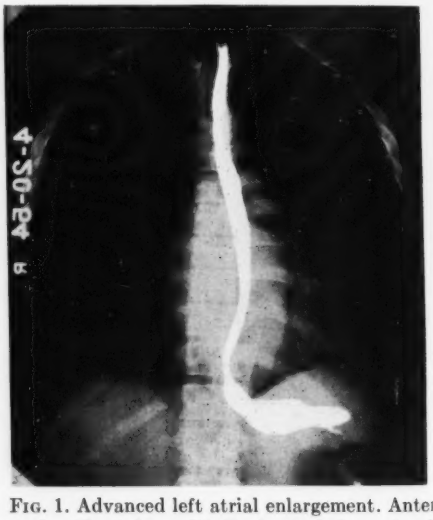
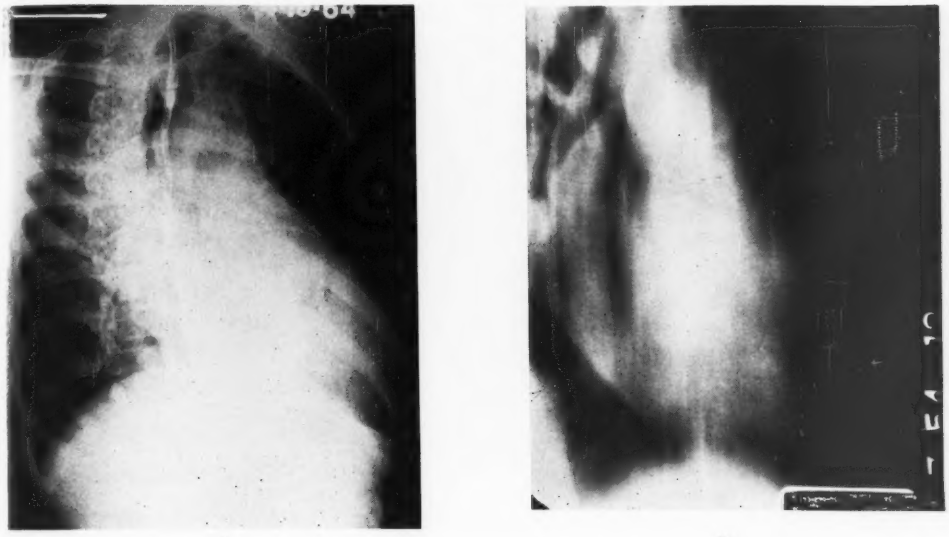
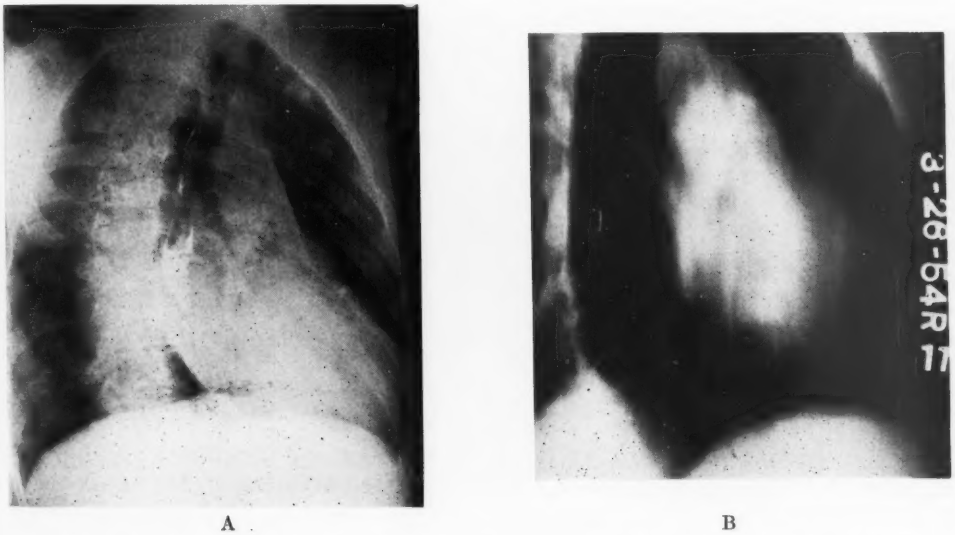


FIG. 1. Advanced left atrial enlargement. Anterior-posterior film taken with Bucky technique showing deviation of barium filled esophagus to the left instead of to the right.



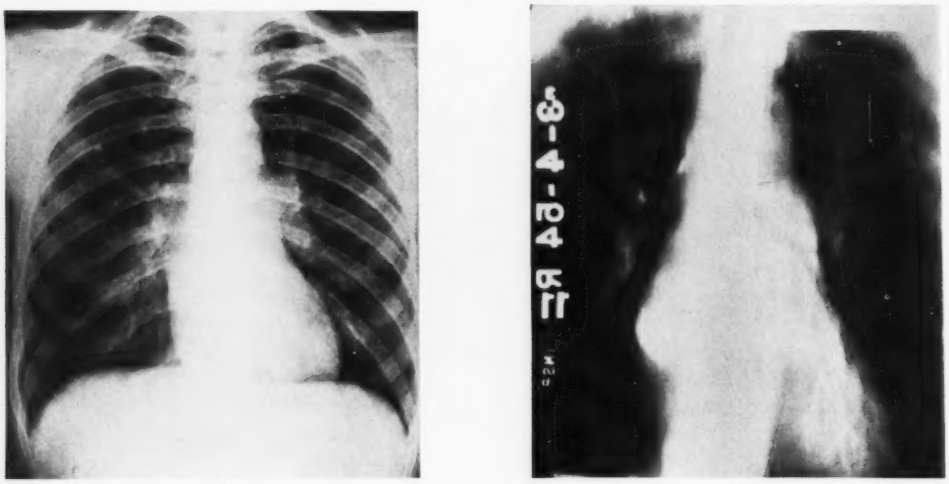
A B

FIG. 2. *A*. Conventional right anterior oblique roentgenogram of the same patient referred to in figure 1. Barium filled esophagus is straight and does not indicate left atrial enlargement, although retrocardiac space is obscured. *B*. Body section roentgenogram of the same patient in the right anterior oblique position. Marked enlargement of the left atrium is clearly shown.



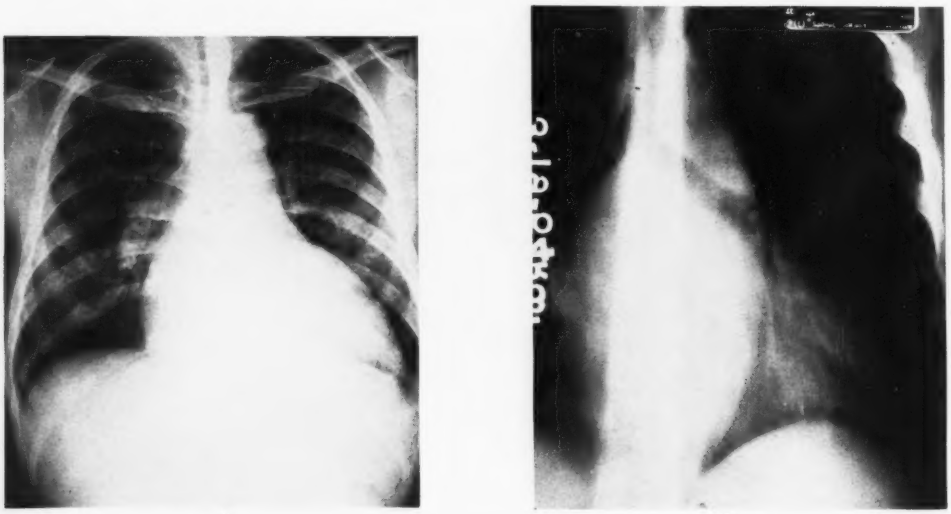
A B

FIG. 3. *A*. Conventional right anterior oblique roentgenogram of patient with advanced mitral stenosis. Barium filled esophagus shows slight posterior displacement. *B*. Right anterior oblique body section roentgenogram of same patient. Note markedly enlarged left atrium not demonstrated by barium column in *A*. Mitral valve calcification is clearly visible.



A B

FIG. 4. *A*. Conventional posteroanterior roentgenogram. Note dense hilar shadows and suggestion of a double contour on the right upper heart border. *B*. Posteroanterior body section roentgenogram showing enlarged left atrium on the right upper cardiac border. Note clear demonstration of the bronchial angle. Hilar masses are clearly identified as pulmonary arteries.



A B

FIG. 5. *A*. Conventional posteroanterior roentgenogram of patient with large left atrium. *B*. Posteroanterior body section roentgenogram of patient referred to in 5*A* showing clear demonstration of the widened bronchial angle.

depends largely upon its impingement on, or displacement of, contiguous structures, particularly the barium filled esophagus and the bronchi. As the left atrium enlarges the following changes take place:

I. *Displacement of the Barium Filled Esophagus.* As the left atrium enlarges it first expands posteriorly, compressing and displacing the esophagus. As a result of the normal eccentric position of the esophagus to the right of the midline and some clockwise rotation of the heart, the barium filled esophagus is usually

displaced to the right as well as posteriorly. This deviation is most easily observed in the right anterior oblique or lateral view. Frequently the esophagus "slips off" or is displaced to the left instead of to the right (fig. 1) so that it does not follow the contour of the enlarging left atrium (fig. 2A). This may be the result of: (1) The occasional normal occurrence of a left eccentric position of the esophagus, (2) concomitant enlargement of the right ventricle and right atrium displacing the left atrium and the esophagus to the left, (3) esophageal adhesions to the left and (4) adhesions to an elongate tortuous aortic arch. In body section films the border of the enlarged left atrium can be seen despite the obscuring shadow of the spine and without dependence on the position of the esophagus (fig. 2B).

Even though the barium filled esophagus is displaced posteriorly it sometimes fails to indicate the degree of left atrial enlargement (fig. 3A). In such cases the appropriate body section film clearly indicates the size of the enlarged left atrium (fig. 3B).

II. *Appearance of the Left Atrium on the Right Upper Cardiac Contour in the Frontal Projection* (*Double Contour*). As the left atrium continues to enlarge it extends to the right, first approaching the right border, and later forming the upper part of the right border above and overlapping the right atrium. In conventional roentgenograms the left atrial border is often ill defined, concealed by the right atrial border or obscured by hilar shadows (fig. 4A). Body section films in the frontal projection at appropriate levels clearly delineate the left atrial border from other structures with which it may be confused (fig. 4B).

III. *Elevation and Compression of the Main Stem Bronchi*. Further enlargement of the left atrium takes place superiorly, widening the bronchial angle from the normal of about 70 degrees, to as much as 100 degrees or more, and sometimes compressing both bronchi. This can occasionally be seen in conventional films but is often not well visualized (fig. 5A). The position of the bronchi can readily be demonstrated by body section films in the frontal projection at an appropriate level (fig. 5B).

Body section radiography might profitably be applied to any of the cardiac and vascular contours when they are obscured by superimposition of other structures. It may aid in determining heart size when the borders are concealed by pulmonary consolidation or pleural effusions. Its use in the differentiation of vascular shadows from other intrathoracic masses is well known to radiologists although not so widely applied as it might be. This includes the differentiation of pulmonary arteries from other hilar masses (fig. 4A and 4B) and the differentiation of aortic aneurysms from other mediastinal masses. Mention has already been made of the demonstration of intracardiac calcification[3] (fig. 3B).

Summary

Body-section radiography is a useful roentgenologic technic which has had little application in the study of the heart. Its use in the identification of left atrial enlargement is described. The method may advantageously be applied to the delineation of other cardiac and vascular contours when they are not clearly defined in conventional roentgenograms.

Summario in Interlingua

Radiographia sectional es un utile technica roentgenologic que ha habite pauc application al studio del corde. Es describite su uso in le identification de allargamento sinistroatrial. Le methodo es usabile con avantage in le delineation de altere contornos cardiac e vascular quando istos non es clarmente definite in roentgenogrammas conventional.

Acknowledgment

The authors would like to express their appreciation for the technical assistance of Mr. Arthur Nossbaum.

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Hemodynamics in Patent Ductus Arteriosus Without a Murmur

By JOHN T. SHEPHERD, M.D., M.Ch., WILLIAM H. WEIDMAN, M.D., EDMUND C. BURKE, M.D. AND EARL H. WOOD, M.D., PH.D.

The clinical and hemodynamic features are described in a 7½-year-old boy who had a patent ductus arteriosus and pulmonary hypertension without a murmur. Values for oxygen saturation of the blood and dye-dilution curves demonstrated that the flow through the ductus was mainly from pulmonary artery to aorta. This was reversed when the patient breathed 99.6 per cent oxygen. Blood shunted from right to left through the ductus could be detected at the right radial artery. Thus retrograde movement of blood occurred in the aortic arch. Clamping of the ductus caused an increase in pulmonary arterial pressure, a decrease in systemic arterial pressure, an increase in arterial oxygen saturation and a change in the arterial dye-dilution curve toward normal. Division of the ductus was followed by clinical improvement.

GIBSON,[1] in 1900, proposed the term "continuous" to describe the characteristic murmur associated with a patent ductus arteriosus. This murmur, which is present throughout both systole and diastole, increases in intensity up to the second heart sound and fades away late in diastole. It results from continuous shunting of blood from the aorta to the pulmonary artery throughout the cardiac cycle.

If a change occurs in the pulmonary arterial pressure relative to that in the aorta, the characteristic murmur may be altered. In infants the pressures in the pulmonary artery and aorta are such that shunting may occur only during systole and a systolic murmur alone is heard. Rarely the pressures in the two vessels may be so balanced that no murmur is heard. The high pulmonary arterial pressure in infancy probably results from persistence of the fetal type of pulmonary vessels with continuation of high resistance to flow through the lungs.[2] As this resistance decreases the characteristic murmur develops; if it fails to decrease, a continuous murmur may never develop. If in later life the resistance increases again, as a result of either increased pulmonary arteriolar resistance or left ventricular failure, the consequent increase in pulmonary arterial pressure may lead to disappearance of the characteristic murmur. In such cases with a reversed shunt or a bidirectional flow through the ductus, the only murmur present may be a diastolic one at the pulmonary area.

Complete absence of a murmur has been noted, but this is uncommon. Keys and Shapiro[3] described a patient in whom a large patent ductus arteriosus was found at necropsy but in whom no murmur was heard during a 10-day period of observation before death. Ulrich[4] reported a case in 1947 in which murmurs were absent and in which an antemortem diagnosis of primary pulmonary hypertension was made. Gilchrist[5] and Campbell and Hudson[6] have described cases in which the continuous murmur disappeared when congestive failure developed. Murmurs were absent in case 2 of the eight cases of patent ductus arteriosus and pulmonary hypertension described by Hultgren and associates.[7] Lyon and Kaplan[8] recently reported on a patient who had a patent ductus arteriosus and in whom no murmur was heard until the child was 16 months of age.

We wish to report on a patient who had a patent ductus arteriosus without a murmur in whom the diagnosis was made at cardiac catheterization; the ductus subsequently was closed surgically.

CASE REPORT

Clinical Data

A 7½-year-old white boy was first seen at the Mayo Clinic in March, 1954. He had been referred by the home physician for diagnosis of a cardia

From the Sections of Physiology and Medicine, Mayo Foundation, Rochester, Minn.

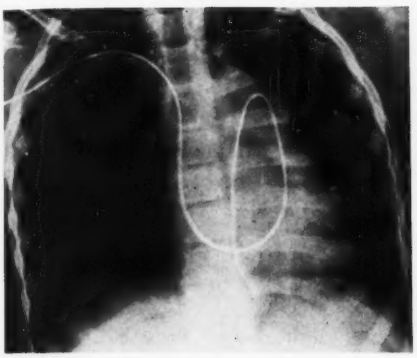

FIG. 1. Cardiac catheter passing from the pulmonary artery through the patent ductus arteriosus into the abdominal aorta.

disability. The physician had examined the patient at birth and had found no abnormalities. However, because the child failed to grow at a normal rate, he had continued to see him at frequent intervals until the patient was 4 years of age, but never had heard a murmur. The physician next had examined this boy in March, 1954, at which time he had observed cyanosis of the nail beds, clubbing of the fingers and toes and roentgenographic evidence of cardiac enlargement. The child apparently had been in good health but was unable to keep up with other children because of dyspnea.

His height was 45 inches and he weighed 42 pounds. He was small for his age and was poorly nourished; however, he was alert and co-operative. The blood pressure in the right arm measured by auscultation was 100 mm. Hg systolic and 85 diastolic. Cyanosis and clubbing were minimal and appeared to be equal in degree in fingers and toes. Precordial bulging and a forceful thrust at the apex were noted. Percussion of the thorax revealed cardiac enlargement. There was no thrill. The second heart sound was accentuated at the second left intercostal space. No murmurs were heard on examination by several observers during a period of four days. The remainder of the physical examination disclosed no abnormalities.

The electrocardiogram gave evidence of right ventricular hypertrophy; thoracic roentgenograms demonstrated right ventricular enlargement as well as enlargement of the pulmonary arterial segment. The value for hemoglobin was 16.8 Gm. per 100 ml. of blood.

The clinical diagnosis was pulmonary hypertension of undetermined nature.

Laboratory Methods

Cardiac catheterization was carried out using a photokymographic recording assembly previously described.[9] Oxygen saturation was determined by both manometric[10] and photoelectric technics.[11] Arterial dilution curves of Evans blue (T-1824) were used in conjunction with the oxygen-saturation values of the blood for the definition of vascular shunts.[12] The recordings during operation were made by means of a mobile photokymographic assembly as described by Hallenbeck and associates.[13]

Laboratory Data

Cardiac catheterization was carried out with the patient under general anesthesia induced by rectal administration of tribromoethanol (Avertin) (100 mg. per kilogram of body weight) and intermittent intravenous injections of thiopental sodium (Pentothal sodium). The data obtained are summarized in the table. With the patient breathing air the venous pressure was normal but pronounced pulmonary hypertension was present. The catheter was passed through a patent ductus arteriosus into the abdominal aorta (fig. 1), where the oxygen saturation of the blood was 85 per cent as compared with 94 per

TABLE 1.—*Cardiac-catheterization Data in a 7½-Year-old Boy With a Patent Ductus Arteriosus and Pulmonary Hypertension Breathing Air and Oxygen*

Position of Catheter Tip	Blood Pressure, mm. Hg		Blood O_2 Content,* Volume Per Cent		Blood O_2 Saturation,† Per Cent		Arterial O_2 Saturation,‡ Per Cent	
	Air	O_2	Air	O_2	Air	O_2	Air	O_2
Right atrium	8/4	11/8	—	—	67	85	92	100
Right ventricle	96/0	118/8	16.2	—	70	85	92	100
Pulmonary artery	104/76	120/82	—	19.8	73	89	92	100
Abdominal aorta§	99/70	118/75	19.0	24.4	85	100	93	100
Radial artery§	100/69	116/75	21.6	—	94	100	93	100
Pulmonary artery wedge	—	12/4	—	—	—	—	—	100

* By Van Slyke analysis.

† By cuvette oximeter.

‡ By earpiece oximeter.

§ Simultaneous samples. Oxygen capacity of blood = 22.2 vol. per cent (Van Slyke analysis).

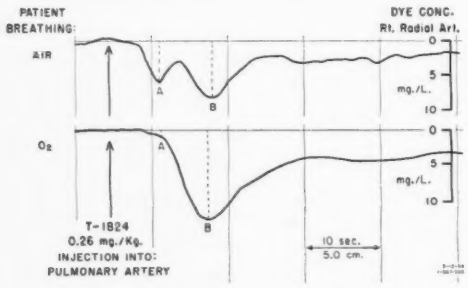

FIG. 2. Dye-dilution curves showing effect of oxygen content of inspired air on the magnitude of the right-to-left shunt through a patent ductus arteriosus in a 7½-year-old boy with pulmonary hypertension. Deflection A is due to dyed blood shunting right to left through the ductus; deflection B is due to dyed blood that has passed through the normal pulmonary circulation. Note greater magnitude of the right-to-left shunt when the patient was breathing air (upper panel) than when breathing 99.6 per cent oxygen (lower panel).

cent in the radial artery. The oxygen saturation of the blood in the pulmonary artery was slightly greater than that in the right ventricle. The data indicated that the shunt, although bidirectional, was mainly from the pulmonary artery to the aorta. It was estimated from the values for oxygen saturation that about 35 per cent of the systemic flow and about 10 per cent of the pulmonary flow was composed of blood shunted through the ductus.

When the patient breathed 99.6 per cent oxygen the blood in the abdominal aorta was fully saturated with oxygen, with 2.2 volumes per cent in physical solution. Therefore, the oxygen-saturation data gave no evidence of a venoarterial shunt at this time but a left-to-right shunt through the ductus was still present as indicated by the increased oxygen saturation of the blood in the pulmonary artery compared with that in the right ventricle (table 1). This shunt amounted to approximately 15 per cent of the pulmonary flow. As the pulmonary arterial wedge pressure was normal, this change in the direction of the shunt was apparently due to reduction in pulmonary arteriolar resistance when the patient breathed 100 per cent oxygen.[14]

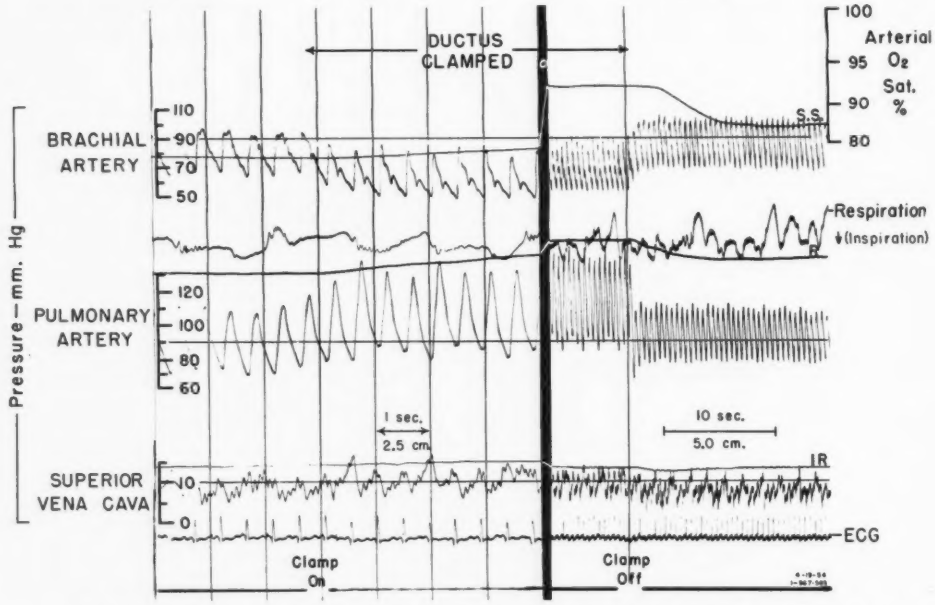

FIG. 3. Hemodynamic effects of occlusion of a patent ductus arteriosus in a 7½-year-old boy with pulmonary hypertension; recordings made during operation. Note reversible increase in pulmonary arterial and central venous pressures, decrease in systemic arterial pressure and increase in arterial oxygen saturation produced by clamping (left panel) and unclamping the ductus (right panel). Note also elimination of the secondary systolic peak in the brachial arterial pulse during closure of the ductus. This secondary peak was presumably due to right ventricular systolic pressure being transmitted to the aorta via the ductus. S.S., R and IR are the single-scale and red and infrared double-scale galvanometer tracings of the oximeter used to record arterial saturation from the pinna of the left ear.[17]

Injections of T-1824 were made into the pulmonary artery with the patient breathing air and repeated with the patient breathing 99.6 per cent oxygen. The dye-dilution patterns were recorded simultaneously and continuously by an oximeter on each ear and a cuvette oximeter from the radial artery (fig. 2). When the patient breathed air, the dilution curves at these sites were similar and showed an abnormally short appearance time with an abnormal initial deflection. This was due to dye shunted through the ductus and reaching the recording sites more rapidly than the major portion of the dye, which passed via the normal route through the lungs. An estimation of the amount of this shunt by the method of Swan and co-workers[15] indicated that about 28 per cent of the systemic blood flow to the upper part of the body came through the ductus. When the patient breathed 99.6 per cent oxygen, a small abnormal initial deflection was noted, indicating a right-to-left shunt of less than 5 per cent of the systemic flow. The prolongation of the disappearance slope indicated a left-to-right shunt of moderate degree.[16] Burchell and associates[14] also have used indicator dye-dilution curves to demonstrate alteration of flow through a ductus when 99.6 per cent oxygen was breathed instead of air. The present case is of interest because the abnormal initial deflection at sites whose arterial blood supply originated from the aorta proximal to the ductus was greater than any previously reported.

The patient was operated on by Dr. J. W. Kirklin in April, 1954. The ductus arteriosus was about the same diameter as the aorta. It was 1.2 cm. in length and 1.4 cm. in width. The pressure in the pulmonary artery was measured before and during temporary clamping of the ductus. Before clamping, the pulmonary arterial pressure was 109/73, the brachial arterial pressure 92/66 and the superior vena caval pressure 12/7, all expressed as millimeters of mercury (fig. 3). One minute after clamping, the pressures were 131/83, 79/49 and 14/8 respectively. Eight minutes after division of the ductus arteriosus the pressures were 134/92, 93/59 and 10/7. At the end of the procedure, 38 minutes after division of the ductus, the pressure in the brachial artery was 85/50 and that in the superior vena cava was 10/6. The contour of the brachial arterial pulse was altered after occlusion of the ductus (fig. 3). Before occlusion the tracing derived from this pulse had a broad summit and two peaks were easily seen. The second peak coincided with the summit of pressure in the pulmonary artery. On occlusion of the ductus the contour of the brachial arterial pulse became normal and no second peak in pressure was discernible. This demonstrated that the right ventricle was contributing to the systolic pressure of the systemic circulation via the ductus.

When the ductus was clamped prior to its surgical occlusion, the systemic arterial oxygen saturation, as measured by the earpiece oximeter, increased from 77 per cent to 92 per cent; it decreased when the clamp was released (fig. 3).

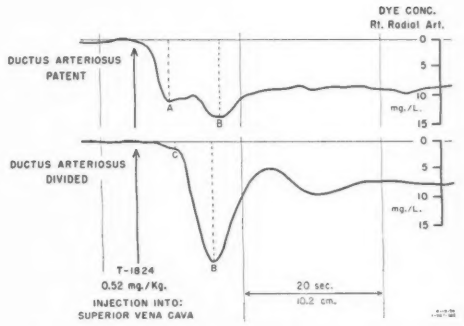

FIG. 4. Dye-dilution curves recorded during operation before and after division of a patent ductus arteriosus in a 7½-year-old boy with pulmonary hypertension. The curves were recorded with the patient anesthetized and the thorax closed before division of the ductus (upper panel) and after division of the ductus and closure of the thorax (lower panel). Deflection A is due chiefly to dyed blood shunting from right to left through the ductus; deflection B is due to dyed blood that passed through the normal pulmonary circulation. Note the large right-to-left shunt before division of the ductus (upper panel) and a normal curve with the exception of a small right-to-left shunt (C) after division of the ductus (lower panel). This residual shunt was probably the result of right-to-left flow through a valvular competent foramen ovale.

Dye-dilution curves recorded with the thorax closed before and at the end of the procedure are shown in fig. 4. The initial curve was similar to that obtained at catheterization with the patient breathing air. The final curve was normal except for a small abnormal deflection preceding the main deflection, consistent with a right-to-left shunt of less than 5 per cent of the systemic circulation. The small shunt after division of the ductus may be due to blood passing through a valvular competent foramen ovale. This shunt was insufficient to cause significant desaturation of peripheral arterial blood.

The patient was kept in an oxygen tent for the first 10 days after operation. He had an uneventful convalescence and was dismissed 16 days after operation. At the time of dismissal, a loud second sound was heard at the pulmonary area. The electrocardiogram still showed evidence compatible with right ventricular hypertrophy of similar degree to that present before operation; however, large inverted T waves recorded from the right side of the thorax suggested increased right ventricular load. There were no clinical signs of right ventricular failure. A note from his physician 3 months later stated that the child was improved but still had

some dyspnea on exertion. The clinical improvement was maintained until 6 months after the operation, at which time the patient died suddenly while eating breakfast. Necropsy was not done.

Comment

Although the occurrence of patent ductus arteriosus without murmurs is rare, it is important to make the diagnosis since operation offers the only hope of cure. If cyanosis or clubbing is greater in the lower extremities than in the upper, the diagnosis can be made clinically. Laboratory methods were employed in the present case because the clinical findings did not reveal the cause of the pulmonary hypertension. The simplest diagnostic method is to compare the oxygen saturation of samples of blood withdrawn simultaneously from the radial and femoral arteries.[7, 14] When a patent ductus is complicated by pulmonary hypertension, however, it is important to know whether or not the pulmonary vessels are capable of dilatation. This can be assessed by measuring the pulmonary arteriolar resistance before and during the breathing of 100 per cent oxygen. Monitoring of pulmonary arterial pressure at operation before and after temporary closure of the ductus is also important because it gives a measure of the increased load on the right ventricle. Postoperative use of mixtures containing large amounts of oxygen may help to reduce the pulmonary arterial pressure by reducing the pulmonary arteriolar resistance, particularly if this has been shown to occur before operation.

It is not known what the reaction of the pulmonary vascular bed is in the usual case of patent ductus arteriosus immediately after birth, but it is probable that sooner or later the arterioles lose their fetal characteristics, with a gradual decrease in resistance to pulmonary flow. Consequently the left-to-right shunt through the ductus increases, occurring in diastole as well as in systole, with eventual elimination of any important shunting from right to left.

In the present case it is probable that the continuation of shunting from right to left was the result of persistence of the fetal type of pulmonary vessels[2] and maintenance of pulmonary hypertension.

Summary

The clinical and hemodynamic features are described in a 7½-year-old boy who had a patent ductus arteriosus and pulmonary hypertension without a murmur.

The clinical diagnosis was pulmonary hypertension of unknown origin. At cardiac catheterization the presence of pulmonary hypertension was confirmed and the catheter was passed through a ductus arteriosus into the abdominal aorta.

When the patient breathed air it was demonstrated by oxygen-saturation values and dye-dilution curves that the flow through the ductus, although bidirectional, was mainly from the pulmonary artery to the aorta. The oxygen saturation of blood in the abdominal aorta was less than that in the radial artery. The diagnostic importance of this is emphasized in cases in which the catheter cannot be manipulated through the ductus.

Dye-dilution curves recorded at both ears and the right radial artery showed that dyed blood passing from the pulmonary artery to the aorta appeared rapidly at these sites. As the origin of the great vessels from the aorta was normal, this demonstrated that a significant degree of retrograde movement of blood occurred in the arch of the aorta.

When the patient breathed 99.6 per cent oxygen the pulmonary vascular resistance decreased and the right-to-left shunt was practically eliminated. This showed that the pulmonary vessels were capable of vasodilatation.

It is postulated that the pulmonary hypertension was due to persistence of the fetal type of pulmonary vessels.

Measurements at operation demonstrated that clamping the ductus caused an increase in pulmonary arterial pressure, with an accompanying decrease in brachial arterial pressure, and an increase in systemic arterial oxygen saturation.

Change in contour of the brachial arterial pulse after clamping of the ductus demonstrated that the right ventricle contributed to the systolic pressure in the systemic circulation via the ductus.

Division of the ductus was followed by clinical improvement that was maintained up

to 5 months after the operation, at which time the patient died suddenly.

Acknowledgement

We wish to thank Dr. J. W. Kirklin, Section of Surgery, for his co-operation. The Evans blue used in this study was supplied through the courtesy of the Warner-Chilcott Company, New York City.

Summario in Interlingua

Es presentate datos clinic e hemodynamic ab le caso de un puero de 7 e ½ annos de etate qui habeva un patente ducto arteriose e hypertension pulmonar sin murmure.

Le diagnose clinic esseva hypertension pulmonar de origine non determinate. Le presentia de hypertension pulmonar esseva confirmate per catheterisation cardiac, e le catheter esseva introducite via le ducto arteriose in le aorta abdominal.

Le valores de saturation oxygenic e le curvas de dilution de colorantes—ambes determinate quando le patiente respirava aere—indicava que le fluxo per le ducto non esseva unidirectional sed progredeva principalmente ab le arteria pulmonar verso le aorta. Le saturation oxygenic del sanguine in le aorta abdominal esseva minus que le saturation oxygenic in le arteria radial. Iste constatation es specialmente importante in casos ubi le catheter non pote esser avantiate a transverso le ducto. Curvas de dilution de colorantes esseva registrate a ambe aures e al dextere arteria radial. Illos monstrava que sanguine colorate viagiante ab le arteria pulmonar verso le aorta arrivava rapidemente al punctos mentionate. Proque le origine del grande vasos esseva normal, iste conducta del sanguine colorate serviva a demonstrar que un grado significative de retrogression de sanguine occurreva in le arco del aorta.

Quando le patiente respirava 99,6 pro cento oxygeno, le resistentia pulmono-vascular deesceva e le derivation ab le dextera verso le sinistra esseva practicamente eliminate. Isto indicava que le vasos pulmonar esseva capace de vasodilatation.

Nos postula que le hypertension pulmonar esseva causate per le persistentia de un typo fetal de vaso pulmonar.

Mesurationes executate durante le operation indicava que un clip super le ducto causava un augmentate pression pulmono-arterial, accompaniate per un reduction del pression brachio-arterial e un augmentate saturation oxygenic del arterias systemic.

Post le application del clip al ducto, il occurreva un cambiamento del contorno del pulso brachio-arterial. Iste facto demonstrava que le ventriculo dextere contribueva al pression systolic in le circulation systemic a transverso le ducto.

Le division del ducto esseva sequite per melioration clinic. Le melioration continuava durante sex menses a qual tempore le patiente moriva subitemente.

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The Relief of Resistant Edema by Utilization of a Sump Phenomenon

By Ferdinand R. Schemm, M.D. and Augusto A. Camara, M.D.*

Fourteen massively edematous patients with either cardiac disease or nephritis, who had hydrothorax and/or ascites, have proved resistant to the usual diuretic measures, but have been relieved of edema by repeated aspirations of fluid from either the pleural or peritoneal spaces. In the intervals between aspirations the fluid of the interstitial space appeared to seep readily into the *sump* from which fluid had just been removed. The repeated aspirations did not result in hyponatremia nor hypoproteinemia in these cases. As a means of by-passing "reluctant" kidneys the utilization of the sump phenomenon has proved simple, safe and effective in some very obstinate cases.

DESPITE the more efficacious control of edema brought about by a better understanding of electrolyte metabolism, the application of acid-base and water balance principles and the development of effective diuretics, there remain certain groups of cardiac and nephrotic patients whose edema remains absolutely or relatively intractable. In our experience, one such group of patients manifest what we shall call the sump phenomenon which will be described in this report.

The authors have collected data on 10 cardiac, 3 nephritic and 1 diabetic patients. Each had an accumulation of free fluid in either pleural or peritoneal spaces. Relief of edema in these patients was achieved by repeated aspirations of fluid from this space, which acted like a "low-pressure" area into which edema fluid readily seeped after each aspiration. In the intervals between aspirations there was little or no change in body weight, but signs of fluid in the *sump* increased, while the degree of peripheral edema decreased. In some of these cases, despite meticulous attention to the regime and repeated doses of mercurial diuretics, no relief of edema could be attained except through repeated aspirations of fluid from the *sump*. In the other cases, utilization of the *sump* for the mechanical removal of fluid proved of value in hastening the relief of edema and shortening the period of hospitalization.

It has been observed that in such patients, recurrence of peripheral edema is preceded by reaccumulation of fluid in the *sump*, and the appearance of edema can be forestalled by repeated tapping.

Most important of all, the authors have seen no deleterious effect of repeated aspirations in these patients.

Method and Material

All but two of the patients reported in this paper were studied in the Metabolic Unit of the Deaconess Hospital. Daily fasting weights in the morning were recorded on a scale sensitive to 100 Gm. Twenty-four hourly urine specimens were collected daily, collections being started and ended at 6 A.M. daily, and their volumes recorded. The daily urinary excretions of chloride, sodium and potassium were determined. Analyses for the same electrolytes were carried out on fluid aspirated from the *sump* each time. The morning following admission, blood specimens were obtained in the fasting state for initial blood chemistry. The chemical determinations included sodium, potassium, chloride, carbon dioxide combining power, blood urea nitrogen and serum proteins. The same analyses were obtained at appropriate intervals and at the end of treatment.

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This work was supported (in part) by a research grant H-150-C, from The National Heart Institute, U. S. Public Health Service.

Published in abstract form in the program of the Scientific Sessions of the Twenty-sixth Annual Meeting of The American Heart Association, Atlantic City, N. J., April 9, 1953, and in the Proceedings of the Central Society For Clinical Research 26: 92, 1953.

* This work was done during a tenure of Fellowship of The American Heart Association.

TABLE 1.—*Clinical Data on Patients Manifesting the Sump Phenomenon*

Patient	Diagnosis	Sump	Aspirations		Mercurial Injections Dose	Edema Weight Loss	Weight Increase Due to Aspirations
			Number	Total amount			
				Liters	*ml.*	*Kg.*	*per cent*
I. Cardiacs							
1. F. J., M, 52	Heart disease, rheumatic; mitral stenosis, mitral insufficiency	Pleural cavity, right	7 in 20 days	13.30	1 3 times 2 twice	15.2	87
2. K. H., M, 62	Heart disease, rheumatic; aortic stenosis, auricular fibrillation	Pleural cavity, right	5 in 13 days	5.30	1 twice 2 once 0.5 twice	10.2	52
3. G. L., M, 18	Heart disease, congenital; marked hypertrophy & dilatation, right ventricle & right auricle; tricuspid insufficiency	Peritoneal cavity	3 in 15 days	9.00	2 4 times 1 8 times	12.0	75
4. B. I., M, 50	ASCVD Diabetes mellitus	Pleural cavity, right	6 in 13 days	4.68	1 3 times	11.0	43
5. B. W., F, 40	Heart disease, rheumatic; mitral stenosis & insufficiency; aortic insufficiency, auricular fibrillation	Pleural cavity, right	4 in 10 days	2.52	0.5 once	15.1	38
		Peritoneal cavity	2 in 3 days	3.28			
				5.80Tot.			
6. B. O., F, 60	Hypertensive ASCVD; auricular fibrillation	Pleural cavity, right	4 in 11 days	2.85	2 4 times 1 once	7.5	38
7. A. L., F, 61	Hypertensive ASCVD	Both pleural cavities	5 in 30 days, 2-L, 3-R	4.74	2 5 times 1 4 times	15.8	30
8. A. W., F. 44	Heart disease, rheumatic; mitral stenosis & insufficiency, auricular fibrillation	Pleural cavity, right	4 in 12 days	2.20	1 3 times	8.3	27
9. C. B., M, 56	ASCVD	Pleural cavity, right	4 in 25 days	3.23	2 6 times 1 once	9.1	35
10. C. D., F, 45	Heart disease, rheumatic; mitral stenosis & insufficiency, auricular fibrillation	Pleural cavity, right	4 in 8 days	2.93	1 twice	2.95	99
II. Nephritics							
1. J. P., M, 3½	Glomerulo-nephritis, nephrotic stage	Peritoneal cavity	5 in 9 days	8.20	0.25 3 times 0.5 once	9.2	89
2. R. W., M, 7	Glomerulo-nephritis, with nephrotic syndrome	Peritoneal cavity	5 in 17 days	22.05	0.5 9 times 1 twice	22.1	99
3. R. D., M, 32	Diabetes mellitus, with Kimmelstiel-Wilson syndrome	Pleural cavity, right	13 in 54	16.45	1 23 times 2 12 times	22.5	73
4. L. A., M, 3	Glomerulo-nephritis, nephrotic stage	Peritoneal cavity	5 in 36 days	4.55	0.5 9 times 0.25 16 times	1.8	252

In two of the patients, immediately following thoracenteses, 50 ml. of deuterium oxide (D_2O) mixed with an equal amount of 5 per cent dextrose in distilled water was infused subcutaneously into the inner aspect of the thigh. Eighteen to 19 hours later, chest fluid and blood were obtained simultaneously for determination of deuterium oxide (D_2O) concentration. The procedures used in these analyses have been described in a previous paper.[1]

Four of the patients, in whom one of the pleu-

TABLE 2. *Electrolyte and Protein Data on Patients Manifesting The Sump Phenomenon During The Period of Study*

Patient	Sodium Out			Plasma Sodium		Protein Out Through Sump	Serum Proteins	
	Via sump	Via urine	Sump sodium	Before aspirations	After aspirations		Before aspirations	After aspirations
	mEq	*mEq*	*Per cent of Total*	*mEq/L*	*mEq/L*	*Gm.*	*Gm/100 ml.*	*Gm/100 ml.*
I. Cardiacs								
1. F. J.	1,638	147	91	136	138	170	7.4 T	8.9 T
							4.4 A	5.5 A
2. K. H.	698	148	82	129	133	48	5.0 T	6.8 T
							4.3 A	5.3 A
3. G. L.	1,239 plus	1,474	45 plus	146	137	248	6.0 T	6.8 T
							3.9 A	4.9 A
4. B. I.	630	934	40	141	143	—	6.1 T	6.3 T
							3.9 A	3.7 A
5. B. W.	338 (chest)	1,262	38	138	136	35 (chest)	6.0 T	6.7 T
	439 (abd)					62 (abd)	3.4 A	3.8 A
						97 Tot.		
6. B. O.	388	743	34	142	144	43	7.9 T	6.8 T
							4.9 A	4.3 A
7. A. L.	666	1,383	33	140	148	174	7.3 T	7.0 T
							4.4 A	4.2 A
8. A. W.	296	642	31	132	141	31	6.3 T	7.0 T
							4.7 A	4.0 A
9. C. B.	435	1,131	27	143	143	71	8.0 T	8.2 T
							5.3 A	5.6 A
II. Nephritics								
1. J. P.	1,149	9	99	140	126	8	2.7 T	3.3 T
					138		1.1 A	1.2 A
					4 days later			
					144			
					2 weeks later			
	Chloride Out			Plasma Choride				
	Via Sump	Via Urine	Sump chloride	Before Aspirations	After Aspirations			
	mEq	*mEq*	*Per cent of Total*	*mEq/L*	*mEq/L*			
2. R. W.	2,485	948	72	101	107	86	4.0 T	4.5 T
							1.4 A	2.1 A
3. R. D.	1,738	3,366	34	110	95	258	3.8 T	5.4 T
							2.1 A	3.6 A

ıl spaces acted as a *sump*, had serial x-ray films f the chest taken during the course of treatment,) show clearing of the fluid after aspiration and s subsequent reaccumulation.

Of the 10 cardiac patients, five were female, and ve were male; all ranging in age from 18 to 62 ears. Five of them had rheumatic heart disease ith chronic valvulitis, four had arteriosclerotic eart disease with or without hypertension, and one ad congenital heart disease.

The patients in the nephrotic stage of glomerulo-ephritis, all males, numbered three, with an age range of 3 to 7 years. The one remaining patient in this series was a young man of 32 who had diabetes mellitus and who also presented the syndrome of Kimmelstiel-Wilson.

Results

In table 1 the over-all clinical data are presented. It gives the number of aspirations performed during the time it took these patients to attain dry weight, the number and dose of mercurial diuretics administered, and the per

cent of actual weight loss attributable to the amount of fluid removed from the *sump*. Note that among the truly resistant cardiac and nephritic patients, the total amount of fluid aspirated accounted for 75 to 99 per cent of the actual weight loss. In the other patients whose clearing of edema was materially hastened by utilization of the *sump*, this figure ranged from 27 to 52 per cent.

Table 2 gives the electrolyte data on 12 of the patients who were studied in the Metabolic Unit. In two of the earlier patients (R. W. and R. D.), treated before a Beckmann flame photometer was acquired, urinary, aspirated fluid and plasma chlorides were determined instead of sodium. The amount of electrolytes, either sodium or chloride, removed via the *sump* varied from 72 to 99 per cent of the total output (sodium or chloride of urine plus that of *sump* fluid) in the patients with intractable edema, and from 31 to 82 per cent in the other patients whose edema cleared more rapidly as a result of repeated aspirations. Plasma proteins (total and albumin) as well as plasma sodium or chloride, before and after repeated aspirations of *sump* fluid was instituted, are also presented in table 2. This table shows, in those cases where the concentration of protein in the aspirated fluid was determined, the total amount of protein removed with the *sump* fluid; the range was from 8 to 258 Gm. Note that despite repeated taps, no harmful dilution of either blood electrolytes or of blood protein resulted.

TABLE 3.—*Data Showing Appearance of D_2O in Sump Fluid Following Its Subcutaneous Administration in Area of Dependent Edema*

Patient	Sump	D_2O Administration		D_2O Concentration 18 Hours Later	
		Amount given subcutaneously	Site	Chest fluid	Blood
		ml.		*Per cent*	*Per cent*
1. F. J.*	Pleural cavity, right	50	Thigh, left	0.124	0.126
2. A. W.*	Pleural cavity, right	50	Thigh, left	0.205	0.205

* No weight change in these two patients during the 18 hours of observation.

The data in table 3 were obtained to show that a tagged material such as D_2O, when introduced subcutaneously into a dependent portion of the body, found its way into the *sump* after a relatively short period of time. D_2O thus administered was found in perfect equilibrium between the chest fluid and blood plasma after 18 to 19 hours.

Case Summaries

Case summaries of the 4 patients who presented *truly resistant* edema that could be relieved only by repeated fluid drainage from a *sump* will be reviewed. In the 10 other patients in this series, clearing of moderately resistant edema was significantly accelerated by the same procedure. The essential data on these patients are shown in the preceding tables.

Case 1. J. P. was a 3½ year old boy whose trouble started with a series of severe upper respiratory tract infections one year prior to hospital admission on Feb. 20, 1949. Onset of edema came two months later, immediately following tonsillectomy. Up to the time of admission, there were several episodes of diarrhea, abdominal pain, fever, upper respiratory tract infection and urticarial rashes. Edema had appeared intermittently, but became persistent and progressive about three months before admission. On admission he was truly anasarcous, with pitting edema from the toes to the scalp, and had a grotesquely protuberant abdomen tight with ascitic fluid. He presented a full-blown picture of the nephrotic stage of glomerulonephritis with albuminuria, cylindruria, microscopic hematuria, hypercholesterolemia, low serum proteins with inverted albumin-globulin ratio and no uremia (blood urea nitrogen 7 mg. per 100 cc.). Marked relief was obtained after the first paracentesis in which 3200 ml. of fluid were removed. As shown in table 1, during a nine-day period, when a total of 8.2 liters were drained from the abdomen, the total edema weight loss was 9.2 kg., or 20 pounds! The aspirated fluid accounted for 89 per cent of this weight loss. The electrolyte data presented in figure 1 demonstrate strikingly the much greater loss of excess body sodium through repeated drainage of the abdomen as compared with the exceedingly small amounts of this electrolyte excreted through the kidneys, despite repeated injections of Thiomerin. Actual calculations show that of the total loss of sodium, 9[illegible] per cent came out through the *sump*. (See table 2.)

This boy was edema-free for a few weeks following

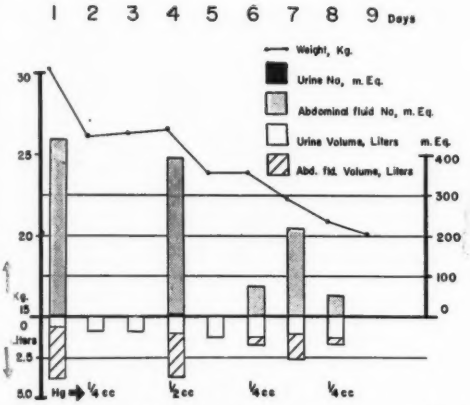

FIG. 1: Graphic representation of data on patient J. P., male, age 3½.

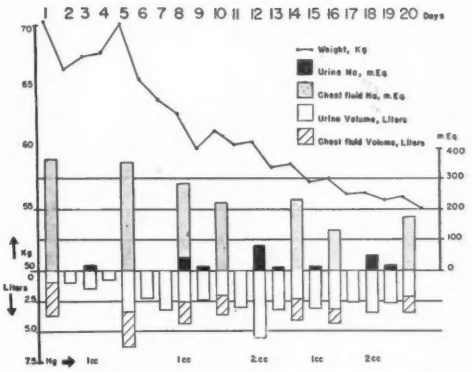

FIG. 2: Graphic representation of data on patient F. J., male, age 52.

discharge. Subsequently, fluid reaccumulated in the abdomen and required tapping every 10 days over a period of many months. At the time of writing, he has been free of edema during the last 12 months.

Case 2. F. J., a 52 year old man, had a high grade mitral stenosis resulting from recurrent episodes of rheumatic fever in childhood. Symptoms of cardiac decompensation started two years before he was seen by us in July, 1952. During the six months immediately preceding our study, he had been repeatedly hospitalized, with no relief following the institution of digitalis therapy, the customary low sodium diet with acid diuretics and frequent doses of mercurial diuretics. Massive right hydrothorax had been aspirated only a few times for mechanical relief of compression of the lung. On admission, he was deeply cyanotic, mentally confused, anasarcous; he had peripheral edema reaching half way up the torso, bilateral hydrothorax, ascites and marked hepatic congestion (lower border of the liver 5 inches below the right costal margin).

He was promptly redigitalized, placed in an oxygen tent and on a high-fluid, neutral diet and ammonium chloride regimen. Even after proper hydration, it was found that injections of Thiomerin resulted in only small diureses of sodium; hence a program of repeated aspiration of the right pleural space was begun. Thoracentesis was performed on the right pleural cavity seven times over the period of 21 days shown in figure 2. The amount of fluid removed ranged from 2800 ml. with the second thoracentesis to 1200 ml. removed during the sixth aspiration. In this patient, the total amount of fluid removed via the *sump*, 13.3 liters, accounted for 87 per cent of the edema weight loss of 15.2 kg. This figure tallies closely with that of 85 per cent of the total excess body sodium removed mechanically through the *sump*, by calculation from electrolyte data. (See table 2.)

As seen in the accompanying series of chest x-ray films (fig. 3), the right pleural space kept refilling with fluid after repeated aspirations. The first plate taken on Aug. 8, 1952, prior to thoracentesis, shows free fluid; following this film, 1700 ml. of fluid was drained. An x-ray film made the same day, shortly after tapping, shows clearing of virtually all fluid. The film taken on Aug. 20, 1952, shows some reaccumulation of free fluid (he had been drained of 1,800 ml. on Aug. 12, 1,200 ml. on Aug. 14., and 1,300 ml. on Aug. 18, 1952). The picture taken on Oct. 6, 1952 shows massive reaccumulation of fluid and a thoracentesis immediately following yielded 2,000 ml. of fluid.

At the time of discharge, this patient was edema-free, but subsequently the right pleural cavity had to be tapped 25 more times at intervals of three to seven days to prevent recurrence of peripheral edema and hepatic passive congestion. Six more thoracenteses were practically dry taps, resulting in withdrawal of only 4 to 30 ml. of fluid. After having been free from recurrence of hydrothorax and from peripheral edema for several months he submitted to cardiac surgery for mitral valvuloplasty in Boston. He died unexpectedly one hour following surgery.

Case 3. R. W. was 7 years old when he came to us in the summer of 1948 with massive anasarca resulting from glomerulonephritis. He had had several bouts of upper respiratory tract infection during the preceding two winters. Edema set in 15 months before admission; it had been preceded for one month by a noticeable change in disposition. There were intermittent spontaneous remissions and exacerbations of edema, but following an episode of vomiting, diarrhea and fever two months prior to admission, edema became persistent and progressively worse. There had been no gross hematuria.

Upon admission the child was almost unbelievably anasarcous (weight 49.2 kg.). The face was full; the palpebral fissures narrowed to mere slits. There was

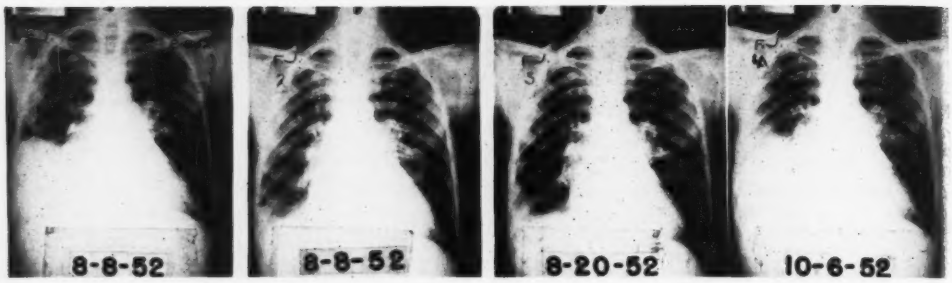

FIG. 3. Serial chest roentgenograms on patient F. J., male, age 52. The first and second chest plates were taken on the same day, before and after aspiration.

deep edema up to the shoulders and axillae. The abdomen (circumference 39.5 inches) was grotesquely distended with free fluid, with some brawny pitting edema of the abdominal wall itself. The scrotum and penis were practically one contiguous globular mass. The legs were so tremendously and tightly swollen with edema that the child had to spread them apart to be comfortable. The complexion was deathly pale.

Admission urine showed 3 plus albumin with a few granular casts, 2 to 5 red blood cells and 5 to 7 white blood cells per high power field. The red blood cell count was 3.4 million and hemoglobin 11.7 Gm. Blood urea nitrogen was 10.5 mg. per 100 cc. The total protein was only 4.03 Gm. and the albumin 1.44 Gm. per 100 cc., despite the preceding high protein feeding. Cholesterol was 492 mg. per 100 cc.

Despite meticulous care in instituting the diuretic regime and in spite of the frequent and repeated doses of mercurial diuretics, 72 per cent of the excess chloride in the body by-passed reluctant kidneys and was removed by mechanical drainage of the peritoneal space (table 2). Figure 4 shows graphically the weight change in relation to paracentesis. Between taps, the weight remained stationary, but was brought down stepladder-wise with each tap. Clinically, while the weight remained stationary between paracenteses, signs of peripheral edema diminished while fluid reaccumulated in the abdomen.

This boy went home entirely free of peripheral edema on the thirty third day, the weight then being 26.7 kg. (edema weight loss of 22.5 kg.). He was seen eight months later at which time he was free of edema and the urine showed no albumin. He had mild recurrence of edema once or twice subsequently for about a year, but he is, at the time of writing, a normally developed 13 year old boy, apparently recovered from glomerulonephritis.

Case 4. K. H. was a 62 year old man who had aortic valvulitis with stenosis and insufficiency attributed to preceding rheumatic infection. He had complained of exertional dyspnoea for many years, and had known of a heart murmur for about eight years prior to hospital admission in August, 1951. On two previous admissions in 1950 and July 1951, under

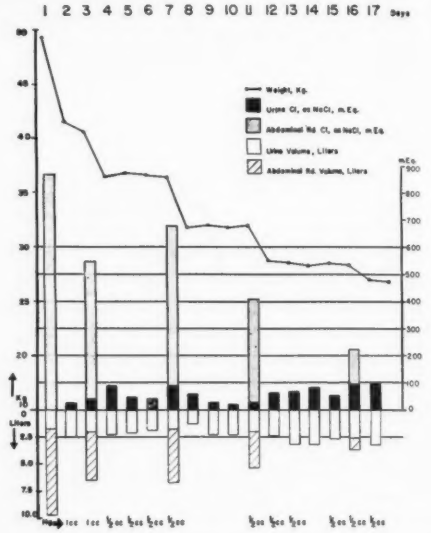

FIG. 4: Graphic representation of data on patient R. W., male, age 7.

a different service, right hydrothorax had been found but thoracentesis was not done. He had complained of orthopnoea on each admission; there was hardly any peripheral edema.

During this admission he incidentally developed an acute cholecystitis for which cholecystectomy was performed and from which he recovered uneventfully. Postoperatively the right pleural space was drained repeatedly at intervals of two to four days. The data are shown graphically in fig. 5. As in the preceding three cases, relatively small amounts of sodium were coaxed out through the kidneys. Most of it was removed mechanically via the *sump*.

Following discharge from the hospital, K. H. underwent further repeated thoracenteses at intervals of one to three weeks for a period of five months. He was entirely relieved of dyspnoea during that period and felt well. Sudden death

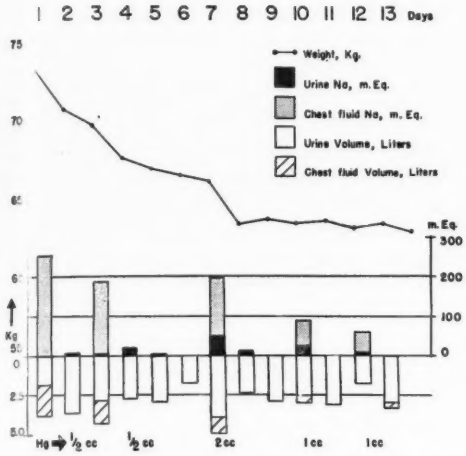

FIG. 5: Graphic representation of data on patient K. H., male, age 62.

came six months later under circumstances not known to the writers.

HISTORICAL COMMENT

Drainage of abnormal accumulations of fluids in body spaces dates back to antiquity. Hippocrates performed it in his day, with often fatal results and the procedure was practiced through the ages and recorded by Galen, Aurelianus, Celsus, Aetius, Avicenna and other notable medical men of history.[2] Among the first to perform abdominal paracentesis during the modern era were Alexander Monro (secundus) and William Hewson, around 1770.[3] Adolf Kussmaul pioneered in the procedure of thoracentesis in modern times, his first operation having been performed in 1868.[4]

The high mortality rate caused by sepsis following either procedure in the early days is understandable. Following the era of Pasteur and Lister, however, abdominal and thoracic paracenteses were not entirely absolved from immediate or remote danger. Capps[5] concluded from his experimental investigations that sudden death following thoracentesis was caused by a pleural reflex resulting in direct cardiac inhibition. Other causes of immediate fatality following thoracentesis were attributed to air embolism[6], pulmonary thrombosis following lung puncture with or without embolism to the heart or brain, and acute pulmonary edema.[7]

Literature on the deleterious effects of abdominal paracentesis is confined mainly to observations in ascites associated with cirrhosis of the liver. Sustained and progressive lowering of blood pressure terminating in shock following drainage of large amounts of ascitic fluid is abundantly described in the literature. Lichtman[8] mentions the not too infrequent rapidly downhill course following a paracentesis. He attributes this to "... the loss of large amounts of protein, electrolytes, water and other vital substances." Cantarow[9] warned against a steady fall in serum protein concentration due to dilution of blood plasma. On the other hand, Mircoli and Ferroni in 1940,[10] reporting studies on cirrhotics conducted over a period of two to eight months, showed that withdrawal of ascitic fluid produced only a moderate reduction in the protein content of the blood in the majority of instances. Restoration of previous levels usually occurred within a week.

Eisenmenger and co-workers,[11] who carried out extensive electrolyte studies on patients with cirrhosis of the liver, reported that in some patients aspiration of ascitic fluid causes an immediate and precipitous fall of serum sodium followed by gradual return to preaspiration levels. Gabuzda and co-workers[12] as well as Nelson and his co-workers[13] have reported the same observations. The latter emphasized the fact that such a drop in serum sodium following paracentesis is more apt to occur in patients with advanced cirrhosis of the liver.

A careful search of the literature has failed to reveal studies of the effect of repeated aspiration on blood proteins and electrolytes in congestive heart failure and glomerulonephritis. Nevertheless, the argument has been advanced that repeated paracentesis or thoracentesis might have the same deleterious effect in those two conditions as in cirrhosis of the liver.

DISCUSSION

The mechanical drainage of free fluid from serous cavities in congestive heart failure and in the nephrotic stage of glomerulonephritis has heretofore been advocated only for relief of compression of the lungs or of oppressive distension of the abdomen. Usually abdominal paracentesis is performed in nephritic patients with ascites in the hope, often vain, that "decompression" of the kidneys will initiate a diuresis.

Observations on the present series of patients have been described in detail in order to introduce the concept of the *sump* and to show that utilization of this phenomenon can be of tremendous help in the management of patients with absolutely or relatively intractable edema. In these cases, the stimuli directing the renal tubules to conserve sodium and water (desoxycorticosterone-like and antidiuretic hormones) are presumably so intense as to make elimination of excess body sodium and water

via the kidneys impossible. Accordingly, to afford relief of edema in such cases, the kidneys have to be by-passed.

The clinical picture of a diminishing peripheral edema while fluid reaccumulated (with no weight increase) in the *sump* just aspirated; the series of chest x-ray films showing refilling of the *sump* following aspirations; and finally, the demonstration that a tagged material (D_2O) administered subcutaneously into an area with peripheral edema found its way into the body space involved, all prove unequivocally the existence of the *sump* phenomenon in the patients described.

In describing the effects of paracentesis in cirrhosis of the liver, Nelson made the same observation that following paracentesis, peripheral edema often decreased during the post-aspiration period while ascites reaccumulated, with no change in body weight. This phenomenon has been observed by many clinicians in patients subjected to periodic aspirations because of ascites due to advanced heart disease or cirrhosis of the liver. There was relief of the tense, shiny distension of the lower extremities after aspiration as the abdominal fullness was recurring. However, the significance of the observation was not grasped, due to the failure to weigh the patients and to appreciate that a shift of edema fluid had occurred. The practice of removing several gallons of fluid only when absolutely necessary was the common practice then, and still is, even now.

It was observed in some of our cases that in order to forestall a recurrence of peripheral edema after dry weight had been attained, it was necessary to aspirate the *sump* at intervals for some months. Failure to do so after 500 ml. to 1500 ml. had collected in the *sump* was followed by the reappearance of peripheral edema, indicating that seepage from the *sump* was occurring in the opposite direction, i.e. out from the *sump* into the interstitial spaces.

Thoracenteses and paracenteses were performed 77 times in this series of 14 patients, and in no instance was the procedure followed by immediate or remote untoward reactions or complications. In those cases with massive hydrothorax (2800 ml. drained in one instance), the precaution of partial air replacement during the procedure, after aliquots of 400 to 600 ml. had been drained, was observed. No striking dyspnoea nor unrelievable pain developed, and no evidence of "pleural reflex" with or without cardiac inhibition was encountered. The procedure of air replacement prevented, of course, any undue negative pressure within the thorax, and produced a hydropneumothorax in which there was rapid absorption of the air and no excessively rapid refilling of the thorax with fluid.

Tight abdominal binders applied over large packs after abdominal paracentesis prevented the occurrence of shock or untoward disturbances even after drainage at one sitting of huge amounts of ascitic fluid amounting in one instance to 33.5 liters in one of our patients (not in this series), a man 62 years of age with arteriosclerotic heart disease, a record amount not exceeded since, in our experience.

In this series was a 7-year-old boy, R. W. with a body weight of 26.4 Kg (when edema-free) from whom more than 8 liters of abdominal fluid were drawn at one sitting without inducing any untoward reaction.

In almost all instances of abdominal paracentesis a prophylactic antibiotic (penicillin unless contra-indicated) was administered the day of and the day following the procedure. If drainage persisted beyond 48 hours the antibiotic was continued without interruption until the paracentesis site was closed. Similar protection was offered when aspiration of a pleural cavity was performed frequently in a frail or poorly nourished patient.

The fact that neither hypoproteinemia nor hyponatremia developed after repeated drainage of *sump* fluid in this series of cardiac and nephritic patients needs to be emphasized. Even though significant amounts of protein were removed by repeated aspiration, protein synthesis by the liver evidently was sufficiently rapid for replacement so that hypoproteinemia did not develop in those with normal serum protein concentrations and there was no further lowering of serum protein values in those who had hypoproteinemia at the beginning of treatment. It should be recalled

hat the concentration of protein in the edema uid, including that of chest and abdominal uid of such patients, is usually not as great s that usually encountered in cirrhotics. This, long with the fact that protein synthesis by he liver in cirrhotics is necessarily impaired, ay account for the difference in our own xperience from that of others[11, 12, 13] who have oted a sharp decline in serum protein concenration following abdominal paracentesis in irrhotics.

With the exception of one (J. P.) who developed a transient lowering of plasma sodium oncentration, none of the patients in our eries developed hyponatremia as a result of repeated aspirations. This is easily understood if one remembers the fact that the fluid removed mechanically is but an aliquot of the total extracellular fluid, and, therefore, contains water and electrolytes (principally sodium) in the proper proportions.

Hyponatremia developing as an immediate, transient complication following paracentesis in cirrhosis of the liver cannot be denied. It is reported in well-documented and detailed electrolyte studies.[11, 12, 13] It will be noted from these reports, however, that this complication is more apt to occur only in the far advanced cirrhotics.

A brief review of the current concepts of electrolyte and water metabolism as well as of edema formation might be of help in understanding the occurrence of this reported complication. As Newburgh[14] has pointed out in an excellent review of the subject, the extracellular fluid in health is characterized by onstancy of concentration of each of its inrganic constituents, and also by relative fixity f its fluid volume. These two features are nder separate control, working through the idneys which are the final guardians of the milieu interne." The reabsorption of sodium s controlled by an adrenal cortical hormone, but the body content of water is governed by the antidiuretic hormone through regulated reabsorption of water. Constancy of concentration of sodium is maintained in health, so that there must be *coordinated* activity of these functions, causing the rate of absorption of sodium to keep pace with the reabsorption of water. At the present stage of our knowledge, we do not know the ultimate nature nor the seat of this *coordinating mechanism*.

In edema, whether it be the anasarca of heart failure, the nephrotic edema of glomerulonephritis, or the ascites of cirrhosis of the liver, the organism has become abnormally geared to maintain an excessively large volume of extracellular fluid. However, except in the far-advanced or deteriorated cases, coordination between the two factors which govern renal tubular reabsorption of sodium and of water is still maintained, as evidenced by persistence of normal concentration of sodium in the extracellular fluid, including edema fluid. In the *far-advanced* cases, be they cardiacs, cirrhotics, or nephritics or patients with a combination of severe heart, liver and kidney damage, whatever the primary difficulty might be, the stimulus for maintenance of an abnormally large volume of extracellular fluid is so intense that when measures such as dietary sodium restriction and mercurial diuretics are instituted for the prevention of further accumulation and for the elimination o excess body sodium, normal sodium concentraf tion in the extracellular fluid is sacrificed for volume; i.e., such patients do lose body sodium, but retain disproportionately excessive amounts of water, resulting in the picture of edema with hyponatremia. In these patients, loss of sodium with resulting hyponatremia may and does occur from administration of mercurial diuretics, due to abnormal losses through the gastrointestinal tract with diarrhea and/or vomiting, or due to aspiration of thoracic or abdominal fluid accumulations. What needs to be emphasized here is the fact that in such far-advanced cases, it is not the aspiration of fluid, but *any* loss of sodium, which can initiate the development of hyponatremia. This fact is often overlooked in attributing hyponatremia solely to aspiration.

Evidently, none of the patients in the series of cardiac and nephritic patients described in this paper falls in the above category. Our patients, with the exception of one who had a transient hyponatremia, all maintained a

normal concentration of plasma sodium after repeated aspirations and while being maintained on a diuretic regimen with moderate dietary sodium restriction.

Summary

Fourteen cases of massive peripheral edema with hydrothorax and/or ascites have proven resistant to the usual methods, but have been relieved by successive aspirations of fluid from either the pleural or peritoneal spaces. The repeated aspirations did not lower the plasma sodium nor protein level; nor were they followed by immediate postaspiration diuresis.

From 27 to 99 per cent of the sodium and water eliminated, to achieve a dry weight, was removed mechanically, rather than coaxed out via reluctant kidneys. In some instances dry weight was achieved with a weight loss which corresponded very closely to the weight of the aspirated fluid. In the intervals *between* aspirations, the signs of fluid in the chest or abdomen *increased* as the signs of peripheral edema *decreased* without any change in total body weight. The fluid of the interstitial space and of the untapped space appeared to seep readily into the *sump* from which the fluid had just been removed.

In most instances after dry weight was reached, the usual regimen, which had been in force from the beginning but had proven ineffective, was effective in preventing reaccumulation of fluid. However, in some instances, it was observed that in order to anticipate or prevent a recurrence of peripheral edema and either hydrothorax or ascites, it was necessary to aspirate the *sump* at intervals for some months. Failure to do so after 500 ml. to 1500 ml. had collected in the *sump* was followed by the reappearance of generalized edema, suggesting that seepage from the *sump* was occurring in the opposite direction.

The advantages of the recognition of the *sump* phenomenon are obvious in those patients in whom, because of intense hormonal stimulation of the renal tubules to conserve sodium and water, loss of edema is impossible in spite of proper attention to the usual regimen. As a means of by-passing reluctant kidneys the utilization of the sump phenomenon has proven simple, safe and effective clinically in some very obstinate cases.

Summario in Interlingua

14 casos de massive edema peripheric con hydrothorace e/o ascites se provava resistente al methodos usual sed esseva alleviate per successive aspirationes de fluido ab le cavitates pleural o peritoneal. Le repetite aspirationes non abassava le nivello plasmatic de natrium o proteina. Illos etiam non esseva sequite per immediate diuresis postaspirational.

In alicun casos le peso del fluido aspirate amontava quasi completemente al excesso que le patiente debeva perder pro restituer su peso non-edematose. In le varie casos, inter 99 e 27 pro cento del natrium e aqua edematose esseva assi eliminate per medios mechanic (e non fortiate a quitar le corpore via le renes reluctante). Durante le intervallos ab un aspiration al altere, le signos de fluido in le thorace o abdomine accresceva in proportion al reduction de signos de edema peripheric durante que le peso total del corpore non se abassava. Le fluido interstitial como etiam le fluido in spatios non-aspirate pareva filtrar sin difficultate a in le spatio ab que le fluido habeva justo essite removite. Le spatio, de facto, ageva como un specie de "cisterna collector."

In le majoritate del casos le peso non-edematose—quando illo esseva establite per le aspirationes de fluido—poteva esser mantenite per medio del regime traditional que—ben que in uso ab le initio—habeva previemente remanite inefficace. Nunc, nonobstante, illo serviva efficacemente a prevenir le re-accumulation del fluido. Sed in alicun casos il esseva observate que pro prevenir le recurrentia de edema peripheric plus hydrothorace o ascites, il esseva necessari aspirar le "cisterna" a intervallos regular durante un periodo de plure menses. Si isto non esseva facite quando un quantitate de 500 a 1500 ml esseva accumulate in le "cisterna", le consequentia esseva un re-apparition del edema general. Isto indicava que il habeva un filtrage de fluido ab le "cisterna" in le direction inverse.

Le avantages del recognition de iste phenomeno del "cisterna" es obvie in le caso de

patientes in le quales le plus stricte observation del regime usual non pote resultar in le suppression del edema proque un intense stimulation hormonal fortia le tubulos renal a conservar natrium e aqua. Como medio de circumvenir le obstaculo de renes reluctante, le utilisation del phenomeno del "cisterna" se ha provate simple, sin risco, e clinicamente efficace mesmo in casos que esseva multo obstinate.

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Mechanisms of Intermittent Ventricular Bigeminy

I. Appearance of Ectopic Beats Dependent Upon Length of the Ventricular Cycle, the "Rule of Bigeminy"

By R. Langendorf, M.D., A. Pick, M.D., and M. Winternitz, M.D.†

In order to analyze the cause for the appearance and disappearance of ventricular premature systoles giving rise to temporary bigeminal rhythm, the electrocardiographic material was divided into two major groups: group A, consisting of ectopic beats with fixed coupling occurring during grossly irregular dominant rhythms, and group B, consisting of ectopic beats with varying coupling occurring during regular dominant rhythms. Analysis of group A, the subject of the present report, shows a definite relationship between the duration of the ventricular cycle and the occurrence of ventricular premature systoles, in that long cycles favor their appearance whereas short cycles tend to preclude it. This "rule of bigeminy" is best explained on the basis of a re-entry mechanism of the ventricular premature systoles. Criteria are given for the differential diagnosis between ventricular premature systoles and aberrant ventricular conduction of supraventricular impulses which is prone to occur under similar circumstances. The analysis of group B is presented in a subsequent report.

BIGEMINY, as a descriptive term[1] of cardiac irregularity refers to a continuous alternation of short and long cardiac cycles, corresponding to the phenomenon of pulsus bigeminus diagnosed at the bedside on palpation of the radial pulse. Such a grouping of ventricular beats may be the result of a number of different mechanisms involving a disturbance of impulse formation or impulse conduction, or a combination of both; an unusual example of the latter as a result of reciprocal beating was presented in a previous report from this department.[2]

The present report is confined to an investigation of the various mechanisms operating in the most common variety, intermittent bigeminy due to ventricular premature systoles. For many years we have been impressed by the observation that in auricular fibrillation the occurrence of ectopic ventricular beats causing bigeminy seems to bear a certain relation to the duration of the ventricular cycle, a fact which has received only scarce attention in the literature.[3, 4] A different group of cases in which intermittence of ventricular bigeminy could be ascribed to a re-entry mechanism was described from this laboratory.[5] Since our attention has been focused on the problem, a third group of cases caused by a parasystolic mechanism was recognized. It seemed to us that the various circumstances under which ventricular bigeminy starts and ends might have wider implications and that the understanding of the factors responsible for initiation and termination of ventricular bigeminy may contribute to the clarification of ectopic premature systoles in general. The first part of our study deals with the factor of ventricular cycle length influencing the appearance and disappearance of ventricular premature systoles. Other causes of intermittence of ventricular bigeminy as revealed in the course of the analysis of the material form the basis of a subsequent paper.

Material and Methods

Thirty-one examples of intermittent ventricular bigeminy caused by ventricular premature systoles were selected from the electrocardiographic files of the Heart Station, the only criterion for selection being a sufficiently long recording to permit a de

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Aided in part by the Michael Reese Research Foundation.

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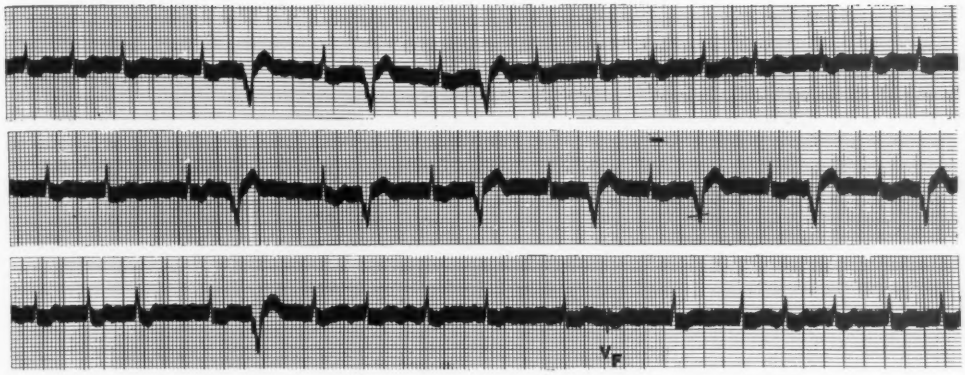

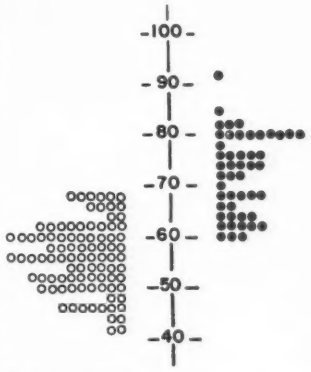

FIG. 1. *Intermittent ventricular bigeminy caused by ventricular premature systoles in auricular fibrillation.* The three strips are portions of a long record in lead II. The conventions in the diagram below the record are as follows: The scale in the center gives the range (in hundredths of a second) of all R-R intervals terminated by conducted (supraventricular beats) in the entire tracing. Those R-R intervals succeeded by a ventricular premature systole are plotted as dots to the right of the scale; those R-R intervals not followed by a premature systole appear as circles on the left of the scale.

Auricular fibrillation is diagnosed in the usual way. In all three strips the sequence of supraventricular beats (average rate 85) is temporarily replaced by bigeminy due to ventricular premature systoles with fixed coupling and uniform contour (except for one beat labeled V_F). Bigeminy starts when the R-R between two conducted beats lengthens; it continues as long as the pause after the premature systole is long; and it ends when this pause shortens. Thus, in *A*, bigeminy consists of a short run, in *B* it continues to the end of the strip and in *C* it terminates with the first premature beat. The beat labeled V_F is a variety of the same phenomenon. Subsequent to a long R-R, an ectopic beat appears at the same coupling as the others, but is intermediate in contour between the dominant and the bizarre ectopic beats. This is a ventricular fusion beat caused by ventricular interference of the ectopic ventricular impulse (occurring because of the long pause) and a conducted auricular impulse which crossed the A-V junction at the same time that the ectopic impulse was released.

The diagram reveals that premature systoles occurred whenever an R-R interval became longer than 0.70 second, and failed to appear when the R-R was shorter than 0.60 second. Within a small range of R-R between 0.60 and 0.70 second, the presence or absence of premature systoles had about the same frequency. Thus, the dependence of bigeminy upon the duration of the cardiac cycle is clearly revealed.

tailed study. No attempt was made at an exhaustive survey of the many records exhibiting this type of rrhythmia. It soon became obvious that on the basis of the spacing of the dominant and ectopic beats the material could be divided into two main roups, namely, (A) a group of 17 records from 14 atients in which the coupling of the premature ystoles was practically fixed and the dominant hythm was grossly irregular, the cases considered n this paper, and, (B) a group of 14 records from 12 atients in which the coupling of the premature ystoles varied but the dominant rhythm was prac- ically regular, the subject of a second communica- ion.

In group A, the irregular ventricular beating had been recorded in long strips. The duration of each ventricular cycle was carefully measured. The various R-R intervals encountered in each case, except the fixed coupling of the ectopic beats, were charted in relation to the occurrence or the absence of a subsequent ectopic beat. Representative examples of such electrocardiograms and graphs are reproduced in figures 1, 2, 3 and 4, and details of the analysis are presented in the respective legends.

RESULTS

In 16 of the records, the ventricular irregularity was marked, in 15 caused by auricular

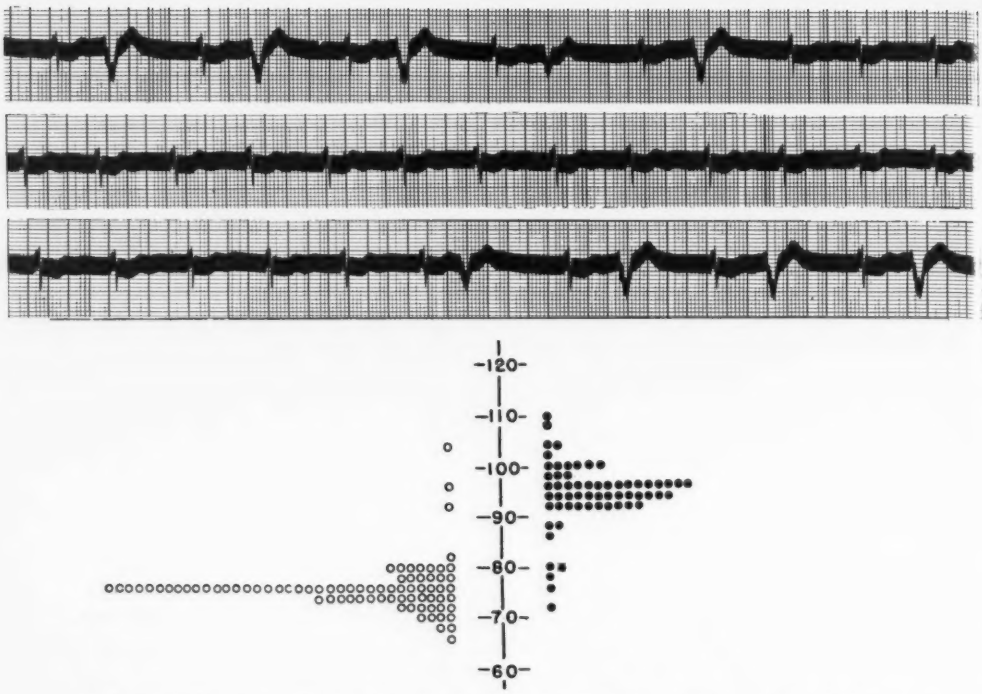

FIG. 2. *Intermittent ventricular bigeminy in auricular fibrillation with A-V dissociation and a slightly irregular A-V nodal pacemaker.* The three strips are consecutive (but not continuous) portions of a long lead II. R-R intervals of the entire tracing—except the short coupling of premature ventricular beats—are plotted in the diagram below. The conventions in the diagram are as in figure 1.

The presence of auricular fibrillation is suggested by the irregular undulations of the baseline and was clearly seen in numerous preceding and subsequent records. In the record shown, there is complete A-V dissociation, the ventricles being under the command of an accelerated nodal pacemaker; temporarily its action is disturbed by ectopic ventricular premature systoles (the bizarre beats) appearing after every nodal beat (ventricular bigeminy). The sequence of nodal beats is otherwise regular (R-R equals 0.74 second, corresponding to a rate of 81), except for the beat ahead of the first ventricular premature systole in the bottom strip; here, the nodal interval lengthens to 0.80 second. The premature ventricular beats show some variation in contour and have with one exception (see below) a constant coupling (0.54 second) to the nodal beats. Their distance to the subsequent nodal beats is 0.94 second, 0.20 second longer than the interval between two consecutive nodal beats. This is due to (concealed) retrograde discharge of the A-V nodal pacemaker by the ectopic ventricular impulse, and possibly to some depression of the nodal pacemaker consequent to this premature extraneous discharge. Thus, at the time of ventricular bigeminy, A-V dissociation persists as in the other parts of the tracing. The exception to be noted concerns the first premature beat in the bottom strip. Its coupling is shorter (0.40 second) and the subsequent nodal interval is longer (1.04 second) than elsewhere. The shortening of the coupling can be ascribed to recovery of impulse conduction in a re-entry path; the prolongation of the nodal interval can be ascribed to a delay of retrograde transmission of the ectopic impulse to the nodal pacemaker, since it occurred earlier in the cycle.

An analysis of the entire tracing, summarized in the diagram, shows that the A-V dissociation was not complete, occasional conducted auricular impulses being represented by the short R-R intervals. The diagram also shows slight irregularity of the nodal pacemaker with variations in its cycle by ± 0.05 second. Finally, the diagram shows clearly the relationship of appearance of ectopic beats to the length of the cycle. With a few exceptions, long ventricular intervals are followed by an ectopic premature beat, whereas short ones appear to preclude its appearance. As seen in the bottom strip of the tracing, even slight spontaneous prolongation of the nodal interval is sufficient to initiate a bigeminus, with subsequent self-perpetuation of bigeminy on account of the long ventricular intervals following each premature beat. This continues until a premature beat fails to appear (upper strip) and the original short nodal interval is restored, which in turn prevents the reappearance of the ectopic beats (middle strip).

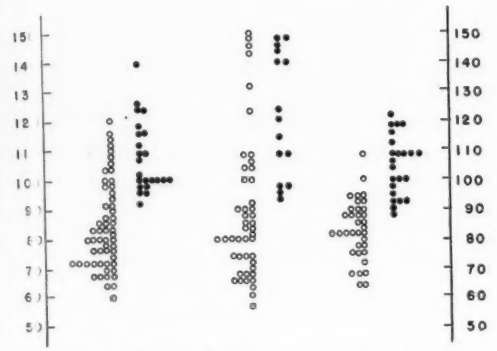

FIG. 3. *Diagrams of three other cases of auricular fibrillation with intermittent ventricular bigeminy* analyzed in the same manner as in figures 1 and 2. The conventions are as in figure 1, except that the scale indicating the duration of the R-R intervals has been moved to the right and left border.

The relation of occurrence of premature ventricular systoles to the long R-R intervals is obvious: no R-R interval shorter than 0.88 second is followed by a bigeminus. However, there is an overlap in the range above 0.90 second, most marked and complete in the middle diagram. This failure of premature systoles to appear when expected can be accounted for on the assumption that on occasion, after a long ventricular pause, re-entry, responsible for the ectopic beats, is initiated as usual, but the impulse is stopped short after entering the re-entry path, or fails to leave it after completion of the sweep (see text). Thus, the ordinary manifestation of re-entry, a premature systole, does not occur. The re-entry, or the attempt at re-entry, remains concealed.

fibrillation (figs. 1 and 3), in one by a sinus arrhythmia (fig. 4). One case of auricular fibrillation (fig. 2) showed less pronounced variations in ventricular cycle length due to the presence of incomplete A-V dissociation with a slightly irregular nodal pacemaker. In no case did the coupling of the ectopic beats vary by more than 0.08 second. The intervals separating the ectopic beats were neither equal nor reducible to a common denominator. The irregularity of the interectopic intervals followed the irregularity of the fundamental rhythm and revealed in no instance an arrangement characteristic of Wenckebach periods.[6, 7] Thus, the possibility of a parasystolic mechanism, without or with exit block, could be ruled out in each case.

In all records a striking consistency was found in that ectopic beats occurred only after long ventricular cycles, and failed to do so when the cycle was short. In fact, a dividing line could be drawn in the ventricular cycle lengths in relation to whether or not an ectopic beat appeared (see charts in figs. 1 to 4). However, exceptions occurred mainly in the range of the longer cycles. Actually, in some cases a considerable overlap was found in that many long R-R intervals failed to be followed by an ectopic impulse. The significance of these findings will be discussed below.

COMMENT

The separation of a certain number of cases with intermittent ventricular bigeminy into a single group was based upon two common findings, the gross irregularity of the dominant rhythm and the fixed coupling of the ectopic beats. Such a combination presents strong support for the concept that premature systoles with precisely uniform coupling are in some way related to, and initiated by, the beat to which they are coupled. While this viewpoint has found wide acceptance in contrast to other past and present viewpoints,[8, 9] no agreement has been reached as to the actual mechanism in operation. Based on experimental evidence, supported by data of neurophysiologic investigation, the theory has been advanced that cardiac tissue may under certain circumstances yield a repetitive response to a single stimulus.[10] In contrast to this assumption stands the theory of a re-entry mechanism[11, 12] presupposing an area of unidirectional block in the periphery of the Purkinje tissue. When such a local impedance to impulse transmission develops, the cardiac impulse, unable to pass through from one direction may reach, enter and traverse it in a reversed direction and restimulate the chamber involved; the result being a premature systole.

The fact, as shown in this report, that the occurrence of a premature systole may be a function of cycle length is hard to reconcile with any other explanation but the re-entry concept. Any alteration in cardiac rhythm which can be shown to depend on the duration and variation of the cardiac cycle, can be viewed in the light of refractoriness and recovery of cardiac tissue. The re-entry concept,

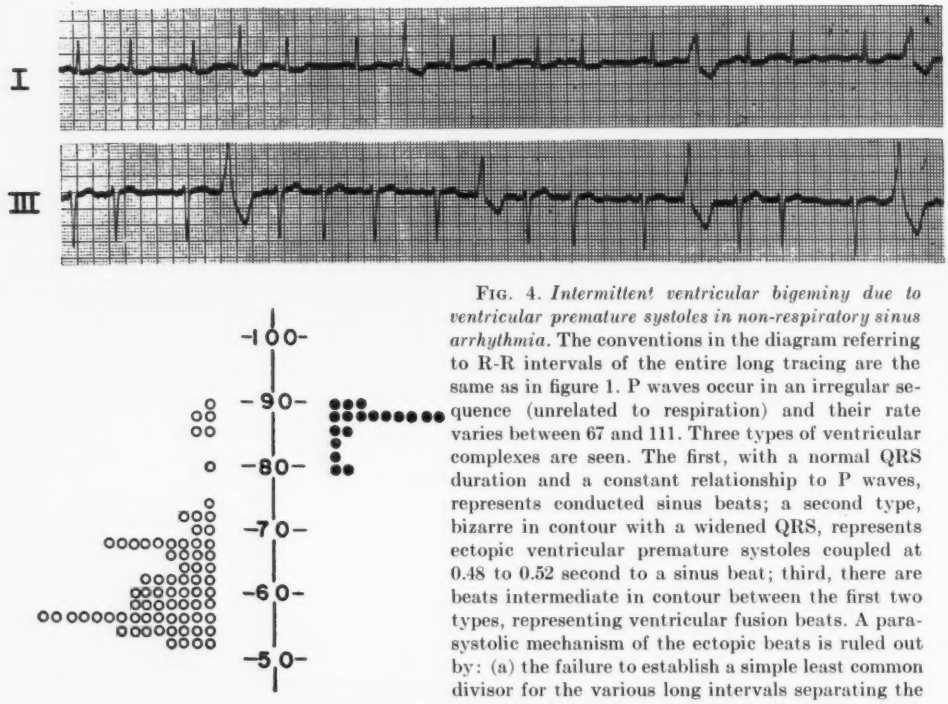

FIG. 4. *Intermittent ventricular bigeminy due to ventricular premature systoles in non-respiratory sinus arrhythmia.* The conventions in the diagram referring to R-R intervals of the entire long tracing are the same as in figure 1. P waves occur in an irregular sequence (unrelated to respiration) and their rate varies between 67 and 111. Three types of ventricular complexes are seen. The first, with a normal QRS duration and a constant relationship to P waves, represents conducted sinus beats; a second type, bizarre in contour with a widened QRS, represents ectopic ventricular premature systoles coupled at 0.48 to 0.52 second to a sinus beat; third, there are beats intermediate in contour between the first two types, representing ventricular fusion beats. A parasystolic mechanism of the ectopic beats is ruled out by: (a) the failure to establish a simple least common divisor for the various long intervals separating the ectopic beats, or the ectopic and fusion beats; (b) the absence of the characteristic spacing of a conduction disturbance of Wenckebach type between the ectopic beats[7]. The appearance of fusion beats is explained on the basis of the marked variability of the temporal relationship of sinus and ectopic impulses due to a pronounced sinus arrhythmia and the relatively long and slightly variable coupling of the premature beats.

The diagram reveals that premature beats did not occur unless the cycle measured 0.80 second or more. The occasional failure of ectopic beats to appear following a long cycle can be accounted for by the implication of a concealed re-entry mechanism as discussed in figure 3.

because it implies a local disturbance of conductivity, can readily be applied to the explanation of the phenomenon under discussion. It would appear that either the pathway leading to the region of unidirectional block (causing the re-entry) is open only after a certain period of rest, or that the region of block itself becomes passable in the reverse direction only after a certain period of rest. The latter assumption is the more likely one since the Purkinje network undoubtedly provides a number of avenues leading to the region of block. Instead of postulating depressed conductivity in all of them, it is simpler to assume that there is but one region of block which is bidirectional at a fast rate, and becomes unidirectional at a slower rate of stimulation. In this way the occurrence of ventricular premature systoles which are dependent upon the length of the cycle can be explained on the assumption of a single region of unidirectional block in the periphery of the conduction system permitting retrograde propagation of the impulse, but only after a long ventricular pause.

Once ventricular bigeminy is initiated in this matter, it tends to persist because of the long pause which follows each premature systole. This pause in auricular fibrillation may be accounted for on the same basis as the ordinary compensatory pause after premature systoles during sinus rhythm, that is, by A-V interference engendered by retrograde transmission of the ectopic ventricular impulse, which

renders the A-V junction temporarily refractory to auricular impulses. Bigeminy usually is stopped when a fibrillation impulse succeeds in traversing the A-V junction at an earlier time and abbreviates this pause. Thus, perpetuation of bigeminy follows the same rule as its initiation.

Exceptions to this "rule of bigeminy" occurred and consisted mainly in the absence of ventricular premature beats after long ventricular cycles. However, this failure of premature systoles to occur when expected may be only an apparent exception. It is possible that on occasion, subsequent to a longer ventricular pause, the impulse may penetrate, as do the others, into the re-entry pathway, but be stopped within the path, or fail to fan out to the rest of the chamber after completion of the re-entry sweep. In either event the ordinary electrical manifestation and consequence of re-entry, a premature systole, will be absent. In support of the assumption of such a "concealed", completed or attempted re-entry are observations of a similar mechanism in reciprocal beating[2] and the unexpected prolongation of the first coupling in instances in which intermittence of ventricular bigeminy can be ascribed to a progressive block within the re-entry pathway, as will be shown in our subsequent paper.[7]

In one instance in which the operation of the "rule of bigeminy" was observed during sinus arrhythmia (fig. 4), the fixed coupling was long and on occasion approached the duration of the variable sinus cycle. This led to competition of the sinus and ectopic impulse for the control of the ventricles resulting in ventricular fusion beats. The fact of a long coupling cannot be used as evidence against a re-entry mechanism, since two or more re-entry sweeps may occur before the impulse spreads out to activate the ventricles.[13] Thus, the occurrence of fusion beats does not always rule against re-entry and in favor of parasystole, just as their absence does not exclude parasystole.[14]

When early beats with bizarre contour and

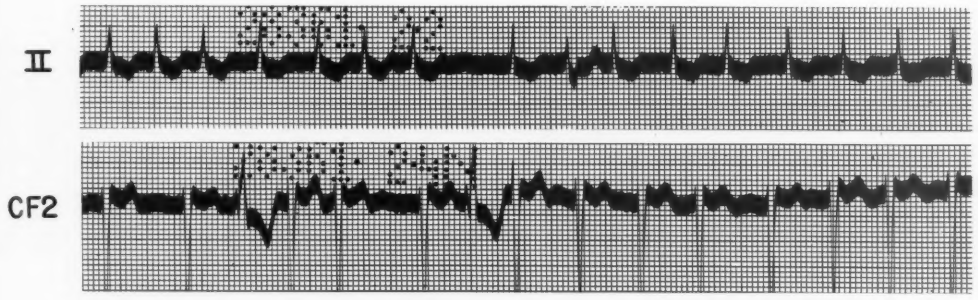

FIG. 5. *A case of auricular fibrillation in which aberrant ventricular conduction of supraventricular impulses imitates the occurrence of ventricular premature systoles related to cycle length.* The ventricular rate is rapid and irregular (130 in the average). Once in lead II, and twice in lead CF_2, ventricular complexes have a prolonged QRS and a contour of a right-sided intraventricular block. In all three instances these beats terminate a short cycle which succeeds an exceptionally long one. The former are of unequal length and not the shortest in the record. This exemplifies that aberrant ventricular conduction, common in cases with rapid heart action is not merely a function of rate, but largely depends on its sudden variations as the refractory phase of the ventricular conduction system lengthens with lengthening of the cycle. Hence, when a short cycle follows a long one, the beat terminating the short cycle tends to show aberrant ventricular conduction.

A similar tendency of ventricular premature systoles to occur in relation to long cycles may be seen in intermittent ventricular bigeminy due to ectopic impulse formation (cf. figs. 1, 2, 3 and 4). The differentiation of the two conditions has practical importance. Fixed coupling and a long ventricular pause following the bizarre QRS-T supports the diagnosis of an ectopic origin of such beats; varying coupling, the contour of right bundle-branch system block, and the absence of a pause after it (as found in this case) are in favor of a supraventricular origin with aberrant intraventricular conduction.

prolonged QRS occur in auricular fibrillation (or auricular flutter with irregular ventricular response) it is of considerable practical importance to distinguish between ectopic ventricular premature systoles and aberrant ventricular conduction of early supraventricular impulses. Such a distinction may sometimes be difficult since under both circumstances the resulting bizarre beat tends to be "coupled" to a beat terminating a long cycle (fig. 5).[4] Whereas the occurrence of an ectopic premature systole in the wake of a long ventricular pause can be ascribed, as outlined above, to partial *recovery* of conductivity in a re-entry path, aberrant ventricular conduction occurring under such circumstances is explained by *impairment* of conductivity in ordinary ventricular conduction pathways caused by prolongation of the normal ventricular refractory phase concomitant with the lengthening of the cardiac cycle. Usually it is the right sided bundle-branch system which is affected by this mechanism.[15] The following three criteria in most instances should permit the correct interpretation of early bizarre beats during irregular ventricular beating. (a) Beats of ectopic origin tend to have a fixed coupling while the short R-R interval of aberrant ventricular conduction tends to vary in a wider range. (b) Aberrant ventricular complexes almost invariably show a pattern of right bundle-branch system block, with QRS prolonged in its terminal portion in contrast to ectopic beats which show a variety of bizarreness, with QRS widened throughout. (c) Unlike premature beats of ectopic origin, aberrant ventricular beats do not give rise to a "compensatory" pause, and it is the absence of such a pause which prevents continuation of aberrant conduction in the form of bigeminy. Aberrant ventricular conduction may, however, continue in the form of consecutive rapid beats with a similar bizarre contour and prolonged QRS duration and thus imitate ventricular paroxysmal tachycardia.[15, 16]

A search of the literature reveals a number of cases with intermittent ventricular bigeminy in which appearance, perpetuation and disappearance of ectopic premature beats follow the stated "rule of bigeminy." The role of the ventricular cycle length is seen in a unique case of Scherf and Schott[17] showing, in auricular fibrillation, parasystole and coupled ventricular premature systoles, the latter occurring exclusively after the long cycles of the parasystolic beats; the only instance of failure of a premature ventricular systole to appear was in a parasystolic beat with a short R-R interval. Likewise, in a case of Holzmann[18] showing a ventricular parasystole and, in addition, ectopic beats with fixed coupling giving rise to temporary bigeminy, the latter was interrupted when the cycle length shortened. A similar mechanism prevails in a case reported by Rachmilewitz and Scherf.[19] Katz[12] illustrates in figure 374 an unusual case of sinus bradycardia and arrhythmia with bigeminy caused by interpolated ventricular premature systoles; intermission of the bigeminy coincides with the shortest ventricular cycle. Figures 111 and 441 are more common examples of the "rule of bigeminy" in auricular fibrillation.

Summary and Conclusions

1. An analysis is presented of selected electrocardiograms with intermittent bigeminy caused by ectopic impulse formation in the ventricles. The material could be divided into two groups. (A) Cases with fixed coupling of the ectopic beats in the presence of grossly irregular ventricular beating. (B) Cases with variable coupling of the ectopic beats in the presence of otherwise regular ventricular beating. Group A forms the basis of this report.

2. In the presence of irregular ventricular beating the appearance of ventricular premature systoles with fixed coupling, their continuation in the form of bigeminy, and the termination of the latter, all tend to depend on the duration of the cycle of the beat to which the ectopic beat is coupled. Lengthening of the ventricular cycle favors the appearance of ventricular premature systoles. The term "rule of bigeminy" is proposed as a short designation of this phenomenon.

3. An adequate explanation of this "rule of bigeminy" can be based on the concept of a re-entry mechanism. Conversely, the existence

o such a rule lends strong support to the view t at re-entry is the mechanism responsible f r premature systoles with fixed coupling in g neral.

4. Whenever there is a rapid and irregular r sponse to supraventricular impulses—in a ricular fibrillation in particular—a beat ter n inating a short cycle subsequent to a long o ie tends to exhibit a bizarre contour and (RS prolongation, caused by aberrant ven- t icular conduction. Criteria are presented for the differential diagnosis between such aberrant s upraventricular beats and ectopic beats of ventricular origin.

5. Cases of intermittent bigeminy of other groups listed under (B) will be the subject of a subsequent report.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

1. Es presentate un analyse de seligite electrocardiogrammas obtenite ab casos de intermittente bigeminia causate per un formation ectopic de impulsos in le ventriculos. Le material es classificabile in duo gruppos. Le prime gruppo include le casos de fixe accopulamento del pulsos ectopic in le presentia de grossier irregularitates del pulsation ventricular. Le secunde gruppo consiste de casos de variabile accopulamento del pulsos ectopic in le presentia de un pulsation ventricular sin altere irregularitates. Le prime de iste gruppos es tractate in le presente reporto.

2. In le presentia de irregularitates del pulsation ventricular, le apparition del prematur systoles ventricular a fixe accopulamento, le continuation de iste systoles in le forma de bigeminia, e le termination del bigeminia, omne iste eventos inclina a depender del duration del cyclo del pulso con que le pulso ectopic es accopulate. Le allongamento del cyclo ventricular tende a coincider con le apparition de prematur systoles ventricular. Nos propone le termino "regula del bigeminia" como designation abbreviate de iste phenomeno.

3. Un adequate explication del "regula del bigeminia" pote esser basate super un mechanismo de re-entrata. Reciprocamente, le existentia de un tal regula supporta le conception que le re-entrata es le mechanismo que es responsabile pro prematur systoles con accopulamento fixe in general.

4. Quandocunque il ha irregular e rapide responsas a impulsos supraventricular—specialmente in fibrillation auricular—un pulso al fin de un breve cyclo que seque un longe cyclo tende a exhibir un bizarre contorno e un prolongation de QRS in consequentia de un aberrante conduction ventricular. Nos presenta criterios pro le distinction diagnostic de tal aberrante pulsos supraventricular e pulsos ectopic de origine ventricular.

5. Casos de intermittente bigeminia con un rhythmo dominante regular e un variabile accopulamento del pulsos ectopic va esser tractate in un reporto separate.

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Mechanisms of Intermittent Ventricular Bigeminy

II. Parasystole, and Parasystole or Re-entry with Conduction Disturbance

By R. Langendorf, M.D., and A. Pick, M.D.

In a previous report dealing with intermittent ventricular bigeminy due to ventricular premature systoles with fixed coupling in the presence of a grossly irregular dominant pacemaker, it was shown that the appearance and disappearance of the ectopic beats were dependent upon the length of the ventricular cycle ("rule of bigeminy"). In the present report, dealing with ventricular premature systoles with varying coupling in the presence of a regular dominant rhythm, the mechanism of ectopic impulse formation is shown to be either parasystole or re-entry, and the intermittence of bigeminy is due to simple interference or to a disturbance in conduction of a parasystolic or of a re-entrant impulse. Intermittent parasystole is illustrated and presented as a possible link between the two fundamental mechanisms of parasystole and re-entry.

IN a preceding report,[1] a group (A) of cases of intermittent ventricular bigeminy was analyzed in which the latter was caused by the occurrence of ventricular premature systoles with fixed coupling during a grossly irregular dominant rhythm. Under such circumstances, intermittence and recurrence of bigeminy were shown to depend largely on the duration of the ventricular cycle. In the course of the study, another group (B) of intermittent bigeminy was identified in cases with a regular dominant rhythm and marked variability of the coupling of the ectopic beats. This group, too, was submitted to extensive analysis and, as in group A, certain conclusions were reached regarding the mechanism involved in the intermittence and reappearance of ventricular premature systoles. The results of this study, and their implications pertaining to the genesis of ventricular premature systoles, are presented in this report.

Material and Methods

The material comprises 14 records from 12 patients with a regular dominant rhythm and intermittent ventricular bigeminy selected on the basis of sufficient material for a detailed study. Since in all cases the coupling of the ectopic beats varied over a wide range, the methods of analysis were those applied customarily in the recognition or exclusion of a parasystolic mechanism.[2] Careful measurements were made of the intervals separating ectopic beats, or ectopic beats and fusion beats, and these were examined as to the presence of a least common divisor, or the presence of a structure characteristic for a conduction disturbance of the Wenckebach type.* Furthermore, the duration of the coupling of the first premature systole upon resumption of bigeminy, whether fixed or variable, was noted; and finally, the cause of intermittence of bigeminy was examined, whether attributable to physiologic refractoriness of the ventricles subsequent to a preceding response, to a conduction disturbance, to intermittence of ectopic (parasystolic) impulse formation or a combination of these mechanisms:

Results

Five representative cases are illustrated in figures 1, 2, 3, 4 and 5, and the analysis of the

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Aided in part by the Michael Reese Research Foundation.

* The characteristic arrangement of the irregularity of rhythm caused by the Wenckebach phenomenon of impaired conduction is as follows[3]: (1) Groups of short cycles are separated by a long cycle. (2) The long cycle separating the short cycles measures less than double that of any of the short cycles. (3) Within the groups of short cycles there is progressive shortening of cycle length. (4) The first cycle after the intermission (long cycle) is longer than the last cycle preceding the intermission.

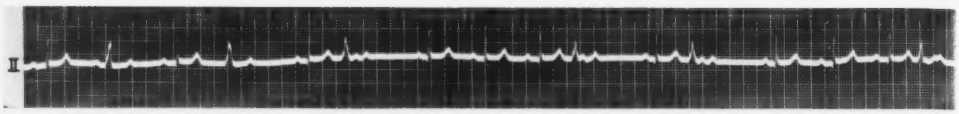

FIG. 1. *Intermittent ventricular bigeminy, due to continuous parasystole, showing progressive shortening and temporary fixed coupling of the ectopic beats.* (Lead II. A continuous long strip obtained on another occasion is reproduced in Katz, *Electrocardiography*[15]). The sinus rate is uneven, varying between 60 and 71. In the first portion of the strip each sinus beat is succeeded by a premature ventricular beat, the coupling of which shortens progressively from 0.92 to 0.52 second. After two successive sinus beats in the middle of the record bigeminy occurs again; here, however, the coupling is fixed (0.52 second) and equal to that of the last premature beat of the first group. Another bigeminus, with the shortest coupling (0.46 second), is seen at the end of the strip. Thus, while the coupling of the premature systole varies within a wide range, the intervals separating them are as follows: 1.76, 1.70, 3.40, 1.70, 1.70 and 3.38 seconds. This establishes the presence of a *continuous ventricular parasystolic pacemaker* operating at a rate of 34 to 35—*a little faster than half the sinus rate.* The two latent discharges of the parasystolic focus (causing the long interectopic intervals) occur 0.04 and 0.06 second respectively following completion of the T wave of a sinus beat and thus within the refractory phase of the ventricles.[2] Thus, in this instance, *intermittent ventricular bigeminy is caused by ventricular interference of sinus impulses with those of a ventricular parasystolic focus.*

The sinus arrhythmia and the development of a fixed coupling appear to be interrelated in the following way: sinus cycles not including a ventricular beat, or starting at the time of an ectopic discharge, are longer than those which include a ventricular beat at a normal P-R distance, or one paired with an ectopic beat (ventriculophasic sinus arrhythmia[16, 17]). Whereas the ectopic rate remains constant, the sinus rate changes depending on the occurrence of an effective ectopic impulse within its cycle. Temporarily the sinus rate becomes exactly twice the rate of the parasystole and bigeminy with fixed coupling ensues.

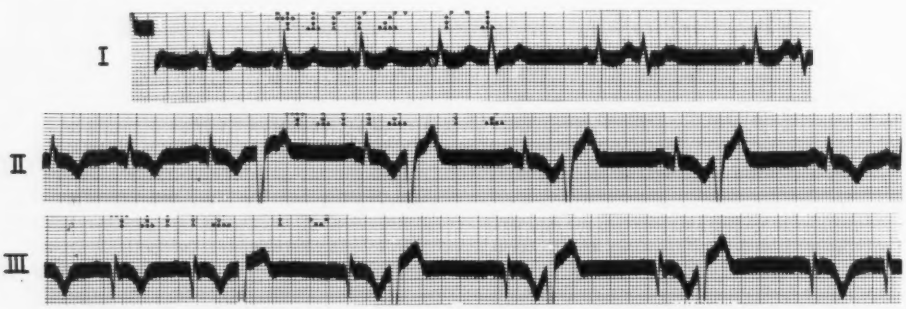

FIG. 2. *Intermittent ventricular bigeminy due to intermittent parasystole, with progressive shortening of the coupling of the ectopic beats* (in a case with healing posterior wall infarction). The regular succession of sinus beats (rate 71) is periodically disturbed by ventricular premature beats. They are similar in contour, but some alterations in the contour of QRS and/or T can be noted in the first premature beat of a series. The coupling varies considerably. There is progressive shortening from the first premature beat (0.56 to 0.54 second) to the last (0.44 second) of a sequence. The intervals separating the premature beats are fairly regular, corresponding to a rate of 36 to 37. This suggests the presence of a *parasystolic ventricular focus* with a rate *a little faster than half the sinus rate.* On this assumption, an ectopic beat would fail to occur after a series of four as a result of the progressive shortening of the coupling, causing a fifth ectopic discharge to coincide with the absolute refractory period following a sinus beat. However, this is not true for the calculated ectopic discharge preceding a series. Note that the first coupling of each series of ectopic beats remains the same.

The factors which determine this unusual appearance of parasystolic rhythm in the form of intermittent ventricular bigeminy are: (a) the rate of the ectopic discharge, which is a little faster than half the sinus rate, (b) the normal refractory period of the ventricle, (c) a temporary breakthrough of a sinus impulse past the barrier of protection of the ectopic focus, or a spontaneous intermittence of the parasystolic activity of this focus. The possibility of temporary exit block of a continuously acting parasystolic focus appeared to be unlikely in view of the fixed coupling of the first ectopic beat of each run of bigeminy and could, in this instance, definitely be ruled out after studying the entire material.

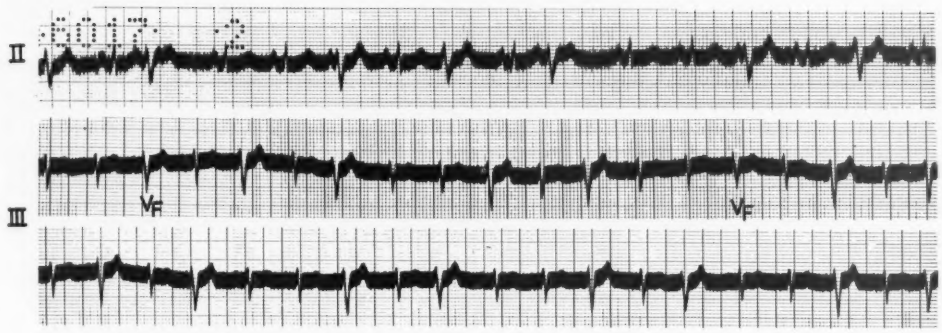

FIG. 3. *Intermittent ventricular bigeminy due to intermittent parasystole showing (a) progressive shortening of the coupling of the ectopic beats and (b) a conduction disturbance of the parasystolic impulses.* The two lower strips are consecutive (but not continuous) portions of a long strip of lead III obtained several hours after the upper tracing (lead II). The sinus rate is 94 in lead II and 107 in lead III. There is an *intermittent ventricular bigeminy*, in that after one undisturbed sinus cycle two or three sinus beats are paired with ventricular premature systoles. The latter vary in coupling and contour. The coupling of a first of a series is fixed in each lead (0.56 second in II and 0.54 second in III) and shortens progressively to 0.38 and 0.44 second respectively. Because in lead III the duration of the first coupling approaches the cycle length of the sinus (0.56 second), the sinus and ectopic impulses occasionally come into competition for ventricular activation with a ventricular fusion beat (V_F) resulting. During bigeminy the intervals between the ectopic beats shorten progressively.

The repetitive occurrence of the premature systoles, their constant coupling, and the occurrence of ventricular fusion beats suggest a *parasystolic mechanism*. A simple parasystole cannot be present since the short intervals are of varying duration and the long intervals are not simple multiples of any short one; nevertheless, the spacing of the ectopic and fusion beats show an arrangement suggestive of a Wenckebach type of block affecting the impulses of a continuous parasystolic pacemaker; however, the fact that the coupling of the ectopic beats initiating each run of bigeminy is fixed, regardless of whether the run of bigeminy consists of two or three couples, rules out a continuous parasystole with conduction disturbance (Wenckebach phenomenon) and suggests an *intermittent parasystole* with conduction disturbance.

On this assumption the intermittence of the resulting bigeminy can be explained in this case in a two-fold way: (a) by temporary intermittence of the parasystolic impulse formation, similar to that seen in figure 2 or (b) by an intermittent "exit block" of the parasystolic impulse. The latter may result from coincidence of the ectopic impulse with normal ventricular refractoriness or may be the result of an abnormal progressive delay of its propagation. This interpretation is supported by the constant coupling of the first of a series of premature systoles, a finding characteristic for intermittent parasystole.

cases is given in the respective legends. The characteristic findings of the spacing of the ectopic beats, the interpretation as to the underlying mechanism, and the cause of intermittence of the ventricular bigeminy are summarized in the accompanying table.

DISCUSSION

All cases included in this group, in contrast to group A,[1] showed marked variations in the coupling of the ectopic beats. Since the cycle length of the dominant pacemaker was constant, it could play no role in the initiation of intermittence of the bigeminy as was the case in group A. The alteration in coupling of the premature systoles occurred either in the form of a progressive shortening (figs. 1 to 3) or progressive prolongation (figs. 4 and 5) before intermittence of bigeminy took place. Only in one case (fig. 1) was the coupling of the ectopic beats temporarily fixed.

Evidently, if *progressive shortening of the coupling* is found during ventricular bigeminy, a re-entry mechanism can be excluded and parasystole has to be suspected. Measuring of the interectopic intervals then permits differentiation between two mechanisms. (1) The long interectopic intervals may be simple multiples of the short ones; this can be considered to indicate *continuous parasystole* with a rate a little faster than half the rate of the dominant pacemaker. Under such cir-

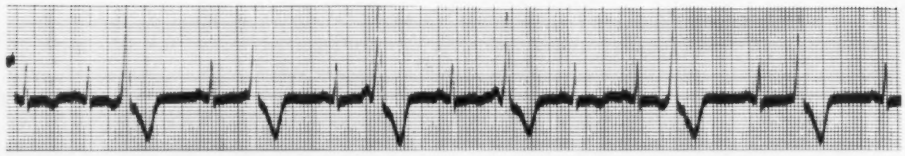

FIG. 4. *Intermittent ventricular bigeminy probably due to intermittent parasystole, with progressive prolongation of the coupling of the ectopic beats.* A regular sinus rhythm (rate 88) is disturbed on three occasions (in the middle of the strip) by premature auricular impulses, the transmission of which to the ventricles is interfered with by the occurrence, just after the premature auricular discharge, of ventricular premature systoles. The ventricular premature beats are part of a sequence of four which starts after the second sinus beat, is interrupted after the sixth sinus beat, and resumed after the seventh. The coupling of the ectopic beats shows progressive prolongation (0.40 to 0.56 second); however, the first coupling of the two runs of bigeminy is fixed. While the short interectopic interval preceding, and that following, the intermittence of bigeminy are almost identical (the difference being 0.04 second), the long interectopic interval that bridges the intermittence is considerably shorter than two short interectopic intervals. This rules against a continuous parasystole with or without conduction disturbance and suggests an *intermittenl type of parasystole* with a rate (42) less than half of the sinus node. A re-entry mechanism with progressive delay in the re-entry path (see fig. 5) cannot be ruled out entirely, but the even spacing of the ectopic beats during bigeminy is definitely in favor of a parasystolic mechanism.

cumstances interruption of bigeminy will take place when parasystolic impulses occurring progressively earlier in the wake of a dominant impulse eventually coincide with the normal refractory phase of the ventricle (fig. 1). When the dominant sinus rhythm is uneven, its rate may temporarily become exactly half the parasystolic rate. As a consequence, the coupling of the ectopic beats may become transiently fixed within the cycle of the sinus beats, an unusual feature in parasystole. In a case like this the diagnosis of parasystole and the exclusion of a re-entry mechanism can be made only if long records are available, as was the case in figure 1. (2) The spacing of the ectopic beats may appear to be quite irregular; however, close examination of the arrangement of the ectopic beats may reveal the characteristic structure of Wenckebach periods. On this basis, too, operation of a regular parasystolic pacemaker can be implied with progressive impairment of the spread of successive parasystolic impulses. Here the intermittence of bigeminy can be ascribed to interference or to "dropped beats," and conditions then become comparable to the familiar mechanisms operating in second degree A-V (and S-A) block. If, at the same time, the coupling of the first ectopic beat of each run of bigeminy is fixed, an *intermittent parasystole*[4] with conduction disturbance can be diagnosed (fig. 3).

If *progressive lengthening of coupling* is found, there are several possibilities to be considered. The spacing of the interectopic intervals may clearly indicate simple parasystole, but this time at a discharge rate just a little slower than half the rate of the dominant pacemaker. Unless the activity of the parasystolic pacemaker itself shows intermittence (as in fig. 4), the bigeminy would be expected to continue for some time, depending on the spacing of the primary pacemaker, before intermittence of bigeminy would be caused by interference of the two competing impulses. If, on the other hand, progressive lengthening of the coupling is associated with a Wenckebach structure of the interectopic intervals, parasystole or re-entry may be operating. Under either circumstance a progressive conduction delay is conceivable in parasystole involving pathways from the ectopic pacemaker to the rest of the myocardium, in re-entry affecting the re-entry path itself or pathways leading to the area of the sweep.[5] In both cases, dropping out of an ectopic impulse causes intermittence of bigeminy. In the case of re-entry the intermittence is expected to follow the longest coupling, and in each run of bigeminy the first ectopic beat would tend to have a coupling

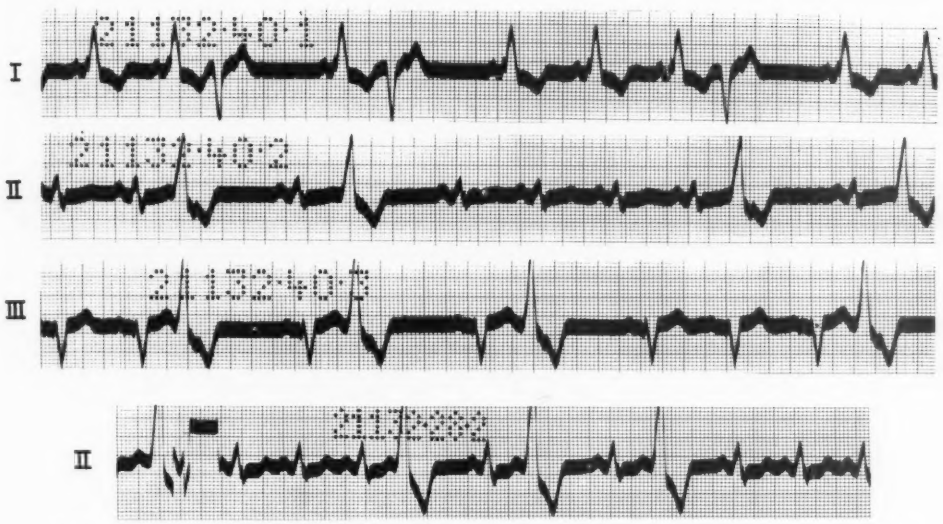

FIG. 5. *Intermittent ventricular bigeminy due to a re-entry mechanism, with progressive prolongation of the coupling of the ectopic beats indicating a conduction disturbance in the re-entry path.* The bottom strip and the upper three strips were obtained on different days. Other tracings of this patient were used in a previous communication.[5] Sinus rhythm is present in all strips, with a rate of 83 in the upper strips and 96 in the lower strip. The sequence of sinus beats revealing the contour of left bundle branch system block is periodically disturbed by premature ventricular systoles of a different bizarre contour giving rise to intermittent ventricular bigeminy. Where premature beats occur in a series of two or three, there is progressive prolongation of their coupling from 0.40 to 0.50 and 0.52 second in the upper strips, and from 0.36 to 0.42 second in the bottom strip. One isolated premature beat toward the end of the uppermost strip has the longer coupling. Note retrograde conduction of those ectopic beats whose short coupling permits the retrograde impulse to reach the atria prematurely, ahead of the sinus impulse.

Intermittent appearance of ventricular ectopic premature beats with variable coupling could suggest a parasystolic mechanism. However, all possible varieties of parasystole can be ruled out in this case. A continuous type is excluded because the spacing of the interectopic intervals has no least common denominator, nor does it show an arrangement consistent with a conduction disturbance of the Wenckebach type. An intermittent type of parasystole is unlikely because the interectopic spacing clearly varies with the sinus rate (compare lowest strip with the others), suggesting a dependence of the ectopic beats upon the sinus impulses. A *re-entry mechanism*, therefore, appears to be the most reasonable explanation. On this basis the progressive prolongation of the couplings preceding the intermittence of bigeminy can be accounted for by a progressive delay of the re-entrant impulse in its pathway, until it fails to complete its sweep. This in turn permits recovery of the re-entry path with repetition of the phenomenon. The unexpected long coupling of the isolated premature systole in lead I does not rule against this interpretation. It may be assumed that, on occasion, an impulse penetrates into the re-entry path without leaving it. Such "concealed re-entry" will lead to prolongation of the re-entry time of a subsequent impulse and will be reflected in a prolongation of the coupling of a following ventricular premature systole.

of equal length and shortest duration; the same would be true for an intermittent parasystole (see below) but would not apply to a continuous parasystole.

An instance illustrating a re-entry mechanism associated with progressive lengthening of the coupling is illustrated in figure 5. In this case re-entry was implied because no consistency in the interectopic spacing was found in the presence of progressive lengthening of the coupling of the premature systoles. Throughout the record, with one exception, the shortest coupling occurs after the intermittence of bigeminy, and the longest just preceding it. The exception is the last premature systole in lead I which has a coupling

TABLE 1.—*Summary of the Analysis and Interpretation of Cases 1 to 5*

	Coupling		Interectopic intervals	Mechanism	Cause of intermittence of bigeminy
	First after intermittence	Mode of alteration			
Case 1	variable	Progressive shortening (temporarily fixed†)	Short: regular Long: multiples	Continuous Parasystole (R-R) < 2(P-P)*	Interference
Case 2	fixed	Progressive shortening	Short: regular Long: not multiples	Intermittent Parasystole (R-R) < 2(P-P)	(a) Interference *and* b) Intermittence of activity
Case 3	fixed	Progressive shortening	Irregular with Wenckebach structure	Intermittent Parasystole (R-R) < 2(P-P)	Intermittence of activity *or* interference, *or* exit block due to conduction disturbance
Case 4	fixed	Progressive prolongation	Short: regular Long: not multiples	Intermittent Parasystole (R-R) > 2(P-P)	Intermittence of activity
Case 5	fixed (except one)†	Progressive prolongation	Irregular. *No* Wenckebach structure	Re-entry with conduction disturbance	Block in re-entry path

* R-R = Parasystolic interval † discussed in text
P-P = Sinus interval

longer than anticipated, and corresponding to the second coupling of the other groups. This apparent inconsistency can be explained by the assumption that the sinus beat ahead of this bigeminus initiated a re-entry which was not completed because the impulse penetrated only partially into the re-entry path. This would represent an unusual variant of "concealed conduction," occurring in a re-entry path and manifested by its effect on the duration of the subsequent re-entry sweep (coupling), analogous to a phenomenon ordinarily encountered in pathways of A-V conduction.[6] A similar mechanism was proposed by Schott,[7] affecting the conduction of parasystolic impulses.

The duration of the coupling of the first premature beat initiating a run of bigeminy was fixed in four of the five illustrated cases. Only in one case (fig. 1) was there a variation exceeding 0.08 second. This and the type of the interectopic spacing left no doubt as to the operation of a continuous parasystole in that instance. Ordinarily, fixed coupling of premature systoles is considered to indicate dependence of the ectopic beat upon the beat to which it is coupled, and a re-entry mechanism can be assumed to be present. However, a repetitive occurrence of a constant coupling is also seen in intermittent parasystole,[8] a condition in which the regular activity of the ectopic focus is periodically disturbed, either by transient disappearance of its "protection," or by spontaneous intermittence of the parasystolic impulse formation. Such fixed coupling is, of course, limited to the first of a sequence of parasystolic beats. Simple cases of intermittent parasystole causing intermittent bigeminy are illustrated in figures 2 and 4; here, the interectopic intervals within the runs of bigeminy are constant. In figure 2, on the other hand, the arrangement of the ectopic beats would indicate intermittent parasystole with conduction disturbance of the Wenckebach type. It would appear that the same mechanism which is responsible for sporadic or repetitive appearance of isolated premature systoles, may, on occasion, initiate continuous

ectopic impulse formation. A series of such ectopic beats, when rapid, constitutes a paroxysmal tachycardia, when occurring at a slow rate, parasystole of an intermittent type. Thus, intermittent parasystole may represent a link between the two fundamental mechanisms of re-entry and parasystole.

The recognition of an intermittent type of parasystole introduces another factor which may be responsible for intermittence of bigeminy, in addition to physiologic ventricular interference and conduction disturbance of the parasystolic impulses. In fact, in the case of figure 3, it cannot be decided which of these three mechanisms causes the intermittence of bigeminy. Moreover, as pointed out before, when the rate of the parasystolic pacemaker is slower than half the rate of the dominant rhythm, so that there is progressive lengthening of the coupling of successive ectopic beats, it may become very difficult or impossible to determine whether a conduction disturbance involves an intermittent parasystole or a re-entry mechanism (fig. 4). The distinction can be made when a Wenckebach structure of the interectopic intervals is associated with progressive shortening of the coupling, since this obviously cannot occur with re-entry (fig. 3).

No case was encountered in our material in which intermittent bigeminy was caused by a continuous parasystole with regular spacing at a rate approaching half the sinus rate, and in which intermittence could not be attributed to the normal refractory state of the ventricles. Such cases are on record (see below), and an "exit block" without the Wenckebach phenomenon has to be postulated to account for the intermittence.

A number of cases can be found in the literature complying with the classification of *parasystolic bigeminy* outlined above. Ventricular bigeminy due to continuous parasystole and intermittence of the bigeminy as a result of the normal refractory period (with progressive shortening of the coupling of the ectopic beats) is seen in a case of Faltitschek and Scherf,[9, case 5] and (with progressive lengthening of the coupling) in two cases of Scherf and Schott,[10, figs. 102 and 103] a case of Vedoya,[11, fig. 5] and a case of Gentile.[12, fig. 1] Intermittent bigeminy due to continuous ventricular parasystole with exit block (with progressive lengthening of the coupling) can be recognized in a case of Scherf and Schott,[10, fig. 109] and with both progressive lengthening and progressive shortening in the same record as a result of marked sinus arrhythmia, in a case of Goldenberg and Scherf.[13, figs. 1 and 2] Unusual instances of intermittent parasystole (without conduction disturbance of the ectopic impulse during the runs of bigeminy) were reported by Scherf and Boyd.[8] Their case 2 shows progressive shortening of the coupling, case 3 progressive lengthening in a case of a parasystolic pacemaker almost identical in rate with that of the sinus node, and bigeminy due to interpolation of the ectopic beats. The difficulty in distinguishing between bigeminy due to intermittent parasystole and re-entry with progressive conduction delay in the re-entry path is well illustrated by the cases of Zander[14] and Scherf and Schott.[10, fig. 130]

A review of the entire material, both of the first part of our study[1] and of the present report, permits the following regrouping and *classification of intermittent ventricular bigeminy due to ventricular premature systoles*, based on the two mechanisms of ectopic impulse formation.

A. *Bigeminy due to re-entry* (1) With *fixed coupling* and intermittence of bigeminy due to critical shortening of the ventricular cycle of the dominant rhythm,[1] (2) With *varying coupling* and intermittence of bigeminy due to a conduction disturbance in the re-entry path.

B. *Bigeminy due to parasystole* with *varying coupling* and intermittence due to (1) The refractory phase of the ventricles following a response to the dominant pacemaker (*interference*), (2) *Exit block* of the parasystolic impulse with or without the Wenckebach phenomenon, (3) *Intermittence of ectopic impulse formation*, spontaneous, or due to temporary disappearance of protection (intermittent parasystole).

Our study and classification do not include cases in which intermittent bigeminy with

fixed coupling of the premature systoles occurred in the presence of a regular dominant rhythm. Although such cases are numerous and actually represent the most common variety of intermittent ventricular bigeminy in clinical electrocardiography, their study seemed redundant, since no insight can be gained into the mechanism of ectopic impulse formation in the face of constant spacing of both the dominant and ectopic beats. For that reason their inclusion in the above genetic classification did not appear warranted. Their mode of initiation and termination of bigeminy remains undetermined. Either mechanism, re-entry or intermittent parasystole with a rate of the parasystolic pacemaker half that of the dominant rhythm, could account for such ectopic beats.

Summary and Conclusions

1. As a continuation of a preceding report on the mechanisms of intermittent bigeminy caused by ventricular premature systoles, an analysis is presented of five selected cases exemplifying a group characterized by a regular dominant rhythm and variable coupling of the ectopic beats.

2. Under such circumstances, ventricular bigeminy may be due either to re-entry or parasystole. Criteria for the differentiation between the two mechanisms are based upon (a) the presence or absence of fixed coupling and (b) the numerical relationship of the interectopic intervals which may point to the presence of a simple parasystole or one complicated by a conduction disturbance of the Wenckebach type.

3. When spacing of the ectopic beats characteristic of a parasystole was found only in the individual runs of bigeminy, but not throughout the record, an intermittent form of parasystole was diagnosed. Under such circumstances the coupling of the first premature beats after the intermittences of bigeminy was fixed. The latter phenomenon supported the diagnosis of intermittent parasystole.

4. Intermittent parasystole appears to represent a link between the two fundamental mechanisms of re-entry and parasystole.

5. Intermittent bigeminy in parasystole occurs when the rate of the parasystolic pace maker approaches half the rate of the dominan pacemaker. If it is slightly faster the coupling of successive ectopic beats exhibits progres sive shortening; if it is slightly slower, th coupling shows progressive lengthening. In termittence of bigeminy occurs as a result o (a) the normal ventricular refractory period (b) a conduction disturbance of the parasystoli impulses, (c) intermittence of ectopic impuls formation, and (d) a combination of thes mechanisms.

6. Differentiation between a re-entry mech anism and intermittent parasystole is no always possible. This is true for both shor runs of bigeminy with fixed coupling an certain cases with progressive lengthening o the coupling.

7. The literature is reviewed for cases with intermittent ventricular bigeminy, and some unusual instances are pointed out, revealing mechanisms similar to those presented above.

8. A classification is proposed of intermittent bigeminy due to ventricular premature systoles based on genetic principles.

Summario e Conclusiones in Interlingua

1. In continuation de un previe reporto super le mechanismos de bigeminia intermittente causate per prematur systoles ventricular, nos presenta un analyse de cinque seligite casos que exemplifica un typo characterisate per un rhythmo dominante regular e un variabile accopulamento del pulsos ectopic.

2. Sub tal conditiones, bigeminia ventricular pote esser causate per re-entrata o per parasystole. Criterios pro differentiar le duo possibile mechanismos es basate (a) super le presentia o absentia de un accopulamento fixe e (b) super le relation numeric del intervallos interectopic que indica le presentia de o un simple parasystole o un parasystole complicate per un disturbation del conduction del typo Wenckebach.

3. Quando le spatiamento del pulsos ectopic esseva del typo characteristic de parasystole sed occurreva solo in le cursos individual de bigeminia e non in le integre registration, nostre diagnose esseva "un forma intermittente de parasystole." Sub iste conditiones le accop-

la ıento del prime pulsos prematur post le in ermittentias del bigeminia esseva fixe. Iste ul ime phenomeno supportava le diagnose de in ermittente parasystole.

4. Intermittente parasystole pare repre- sı ıtar un nexo inter le duo mechanismos fu ıdamental de re-entrata e parasystole.

5. Bigeminia intermittente in parasystole o curre quando le tempo del pacemaker para- sy stolic approcha medie le tempo del pacemaker d minante. Quando le tempo del pacemaker p rasystolic excede illo del pacemaker domi- n nte levemente, le accopulamento de succes- sive pulsos ectopic exhibi un accurtamento progressive; in le caso contrari, le accopula- mento exhibi un allongamento progressive. Intermittentia de bigeminia occurre in conse- quentia (a) del normal periodo refractori ventricular, (b) de un disturbation conductional del impulsos parasystolic, (c) de intermittentia del formation de impulsos ectopic, e (d) de un combination de iste mechanismos.

6. Le differentiation inter un mechanismo de re-entrata e intermittente parasystole non es semper possibile. Isto es ver tanto pro breve cursos de bigeminia con accopulamento fixe como etiam pro certe casos con allongation progressive del accopulamento.

7. Es presentate un revista del litteratura in re casos de intermittente bigeminia ventricular. In isto nos presta attention specialmente a alicun casos inusual que exhibi mechanismos simile a illos reportate in le presente studio.

8. Super le base de principios genetic nos propone un classification del casos de inter- mittente bigeminia causate per prematur systoles ventricular.

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The Effect of Intravenous Protoveratrine on Digital Pulse Volume and Digital Skin Temperature in Hypertensive Patients

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The change in digital pulse volume and skin temperature was observed after intravenous protoveratrine in 25 studies. A significant increase in the average pulse volume of the finger was noted but the range of change was large. The average change of pulse volume in the toe was not significant. A slight increase in the finger skin temperature was noted. "Vasodilatation" of the hand and feet was not the only factor resulting in a fall in blood pressure since it did not occur in all patients.

PROTOVERATRINE, a purified alkaloid from veratrum album, has been known since 1890[1] and has been found to lower the blood pressure in patients with arterial hypertension. As part of a general study of protoveratrine, it seemed important to determine the change, if any, in the peripheral circulation in hypertensive patients during the effect of this drug. The purpose of this study, therefore, is to present data relevant to the peripheral circulation following the intravenous injection of protoveratrine.

A fall in systemic blood pressure could logically result from dilatation of the peripheral arterioles, a decrease in cardiac output, or a combination of the two. It is not clear from the reports in the literature how veratrum or protoveratrine lowers the blood pressure in man. Investigators have used different preparations of veratrum, both crude and purified, and different methods of administration which make comparison difficult. Hewlett[2] concluded in an early study of eight cases that fall in blood pressure produced by adequate doses of a tincture of veratrum viride by mouth was not accompanied by a change in the pulse form or pulse volume of the extremity. Wilson and Smith[3] described an increase in size of the retinal arterioles after the intramuscular injection of an extract from veratrum viride in a patient with toxemia of pregnancy. Freis and his coworkers,[4] using intramuscular veratrum viride extract, found in a study of six cases, a variable change in blood flow to the forearm or in the lower leg. Using the same drug, seven patients were studied and the cardiac output was found to remain the same in patients without congestive heart failure, but increased in two patients after veratrum viride in whom congestive heart failure was present. Myers and associates[5] noted an average fall of 27 per cent in the cardiac output in 18 patients 15 minutes after intravenous protoveratrine, at the time of maximal blood pressure fall.

Evidence has been presented to indicate that renal clearance of para-aminohippurate increases in some patients after protoveratrine at a time when a moderate decrease of blood pressure occurs. Increased renal blood flow from arteriolar dilatation in the kidneys has been postulated to explain this change.[6, 7]

Direct observation of arteriole size is difficult in man so that it is usually necessary to resort to measurements which are indirect in estimating "vasodilatation." Digital pulse volume has been demonstrated to correlate closely with the calculated digital blood flow in

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We are indebted to Dr. Kenneth Kohlstaedt of the Eli Lilly & Company for a grant-in-aid and for generous supplies of protoveratrine as Provell Maleate used during this study. We are also indebted to Dr. Carl Bunde, Pitman-Moore Company, Indianapolis, Indiana for a grant-in-aid and for parenteral solution and tablets of protoveratrine supplied under the trade name of Veralba.

This study was supported in part by a grant from the U. S. Public Health Service (H-633) and by a generous donation from Stephen S. FitzGerald.

the same individual[8, 9] Digital skin temperature has been observed to change in the same direction as digital blood flow.[9-12] This study was planned to determine simultaneously: (1) The pulse volume in the finger and toe (2) The skin temperature of the finger and toe, in order to judge whether arteriole dilatation occurs in the extremities at the time of the reduced blood pressure induced by protoveratrine.

Method

Twenty-five separate studies have been made on 22 hospitalized patients with hypertension. These studies were made with the subject recumbent in a constant temperature room and the extremities exposed one hour at 68 to 70 F before the test was done. The heart rate was determined by counting the radial pulse for 15 seconds. The systolic and diastolic blood pressure were determined by the usual auscultatory method, using the method as suggested by the American Heart Association.[13] After control observations a dose of protoveratrine was given, which had been found previously to result in a decrease of blood pressure to normal or to a figure near normal in that individual. The dosage ranged from 0.12 to 0.23 mg. The dosage of protoveratrine and the change in blood pressure were similar to the dose used and the change observed at the time of cardiac catheterization, performed on a different day when the hemodynamic effect of protoveratrine was determined.[6] Observations were made at the end of the control period and at 5, 10, 20 and 30 minutes after the injection of the drug. In order to determine the effect of maximal response, heat was then applied to the body to induce reflex "vasodilatation" of the extremities in 17 patients. This was accomplished by means of an electric blanket over the body (12 patients) or the arm was immersed in warm water to the elbow (5 patients) for 30 to 90 minutes and the observations were repeated. The effect of heating the body without having given protoveratrine first was not determined in these subjects.

The age range of the patients was from 21 to 62 years, 12 were women and 10, men. In 19 patients the initial study was made during the first hospitalization and the patient had received oral protoveratrine for less than seven days. Three patients underwent a second study 6 to 12 months following the initial study during which time the patient had been maintained on protoveratrine. One of the patients had a sympathectomy four years before the observations were made.

The digital plethysmographs were recorded from the second toe and the fifth finger by means of the method previously described.[14] Metal cups 4.5 cm. in length with a volume of 18 ml. were applied over the fifth finger and the second toe and sealing was accomplished by the use of a caulking compound. These cups were connected with the transducer by

TABLE 1.—*Degree and Direction of Change of the Blood Pressure, Pulse Rate, Digital Pulse Volume and Digital Skin Temperature, also Standard Deviation of the Difference, Standard Error of the Difference and the t Value*

		Diff.	Per Cent Diff.	Standard Deviation of Difference	Standard Error of Difference	t value	Direction of Change		
							plus	minus	0
Systolic blood pressure									
Control	216								
5 min.	178	−38	−17.8	31.5	6.3	6.1*	2	22	1
10 min.	150	−66	−30.6	42.6	8.5	7.8*	1	24	0
20 min.	146	−70	−32.6	41.0	7.9	8.9*	0	25	0
30 min.	160	−56	−26.2	28.3	5.7	10.0*	0	25	0
Diastolic blood pressure									
Control	134								
5 min.	106	−28	−20.8	23.1	4.6	6.1*	1	24	0
10 min.	94	−40	−30.2	30.3	6.1	6.7*	1	24	0
20 min.	91	−43	−32.1	24.9	4.9	8.9*	1	24	0
30 min.	99	−35	−26.2	22.6	4.5	7.8*	1	24	0
Pulse rate									
Control	78								
5 min.	70	−8	−10.2	10.5	2.1	3.7*	5	18	2
10 min.	61	−17	−21.8	10.7	2.1	7.8*	2	23	0
20 min.	59	−19	−24.2	13.0	2.6	7.2*	1	24	0
30 min.	61	−16	−20.7	12.8	2.5	6.3*	1	23	1
Digital pulse volume left 5th finger									
Control	2.7								
5 min.	4.9	+2.2	+83.9	3.2	0.6	3.5*	20	4	1
10 min.	4.5	+1.8	+68.6	2.5	0.5	3.7*	17	4	4
20 min.	4.6	+1.9	+71.2	3.1	0.6	3.1*	19	5	1
30 min.	4.6	+1.9	+72.3	3.3	0.7	2.9*	18	5	2
Digital pulse volume right 2nd toe									
Control	1.2								
5 min.	1.6	+0.4	+37.3	1.2	0.2	1.8	13	3	9
10 min.	1.6	+0.4	+35.6	1.2	0.2	1.7	11	4	10
20 min.	1.6	+0.4	+32.2	1.2	0.2	1.6	12	3	10
30 min.	1.7	+0.5	+40.7	1.2	0.2	1.9	16	4	5
Finger skin temp. degrees F above normal control									
Control	12.7								
5 min.	13.4	+0.7	+5.6	3.4	0.7	1.0	16	9	0
10 min.	14.3	+1.6	+12.7	4.2	0.8	1.9	17	8	0
20 min.	14.6	+1.9	+14.3	4.6	0.9	2.0	15	9	1
30 min.	15.4	+2.7	+21.6	6.1	1.3	2.1*	16	9	0
Toe skin temp. degrees F above normal control									
Control	4.9								
5 min.	4.9	0.0	0.0	4.7	0.9	0.0	7	17	1
10 min.	4.9	0.0	0.0	4.7	0.9	0.0	8	16	1
20 min.	4.6	−0.3	−7.1	4.9	1.0	0.4	11	11	3
30 min.	5.0	+0.1	+2.2	3.1	0.6	0.2	11	11	2

*t—statistical significance. Started values are statistically significant at the 0.05 level.

means of thick rubber tubing. The pulse excursions were determined by measuring three to ten pulsations on the record within a period of one minute before or after the designated times of observation. This was necessary because of fairly frequent artifacts from the plethysmograph. The skin temperature recordings were done by an automatic recording potentiometer (Brown Instruments—Minneapolis Honeywell Regulator Co.). The skin temperature was recorded from the palmar surface of the thumb and the plantar surface of the great toe and the difference between these and the room temperature was noted.

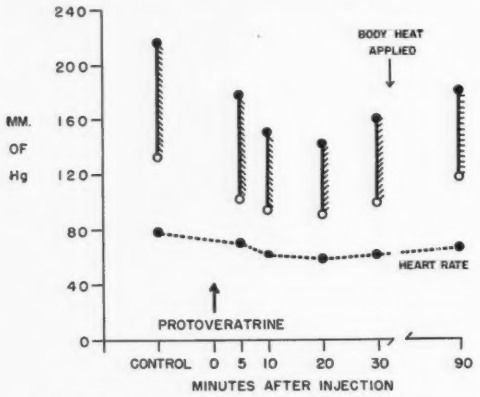

FIG. 1. The average change of the blood pressure and heart rate, 25 observations in 22 patients after intravenous protoveratrine. This was followed by the application of body heat in an effort to produce reflex "vasodilatation."

RESULTS

The average change in blood pressure, heart rate, digital pulse volume and digital skin temperature after intravenous injection of protoveratrine is summarized in table 1 and illustrated in figures 1, 2, 3, 4 and 5. Both the systolic and diastolic blood pressure values were lowest 10 to 20 minutes after the intravenous injection of protoveratrine and were 30 to 32 per cent less than the control values. The change in the digital pulse volume of the finger was about four times as great as that in the toe and the change was maximal in the finger, five minutes after the drug, at which time the pulse volume had increased 84 per cent. It was still 72 per cent above the control

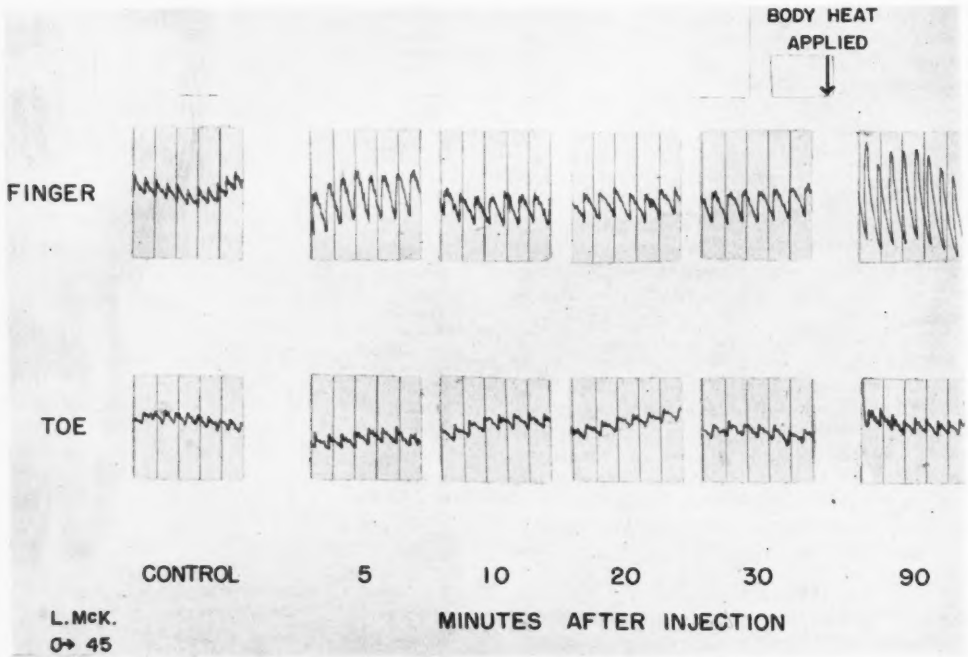

FIG. 2. The digital plethysmograph from a representative patient before and after intravenous protoveratrine. Body heat was then applied to induce reflex "vasodilatation."

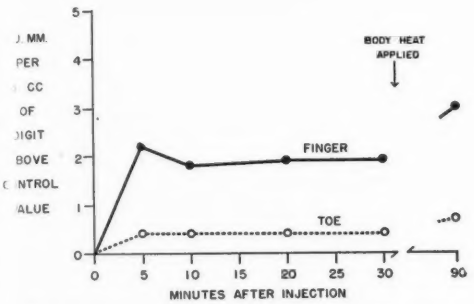

FIG. 3. Average change of the digital pulse volume, 25 observations in 22 patients after the intravenous injection of protoveratrine as compared with the control value. Body heat was then applied to induce more "vasodilatation."

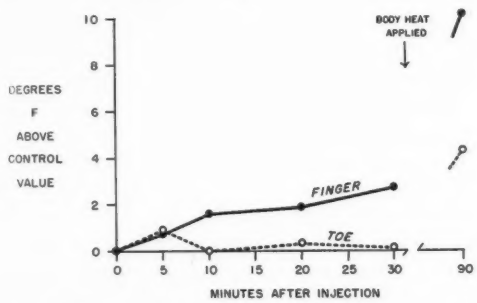

FIG. 4. Average change in the finger and toe skin temperature in 25 observations in 22 patients after application of body heat followed intravenous protoveratrine.

value at the end of 30 minutes. The increase in pulsation in the toe was small and was similar throughout the four periods. The increase in skin temperature was more apparent in the finger than in the toe and was a gradual rise of 0.7 to 2.7 F. The change in the skin temperature of the toe was not significant.

The change in systolic and diastolic blood pressure and the heart rate were highly significant as evidenced by the t values (table 1). The increase in the digital pulse volume of the finger was also significant at the level of 0.05. The calculation of the t value of the digital pulse volume in the toe was not significant at the 0.05 level although the fact that the changes at 5, 10, 20 and 30 minutes were all in the upward direction would suggest that this change was probably significant. The same is true of the change in finger skin temperature

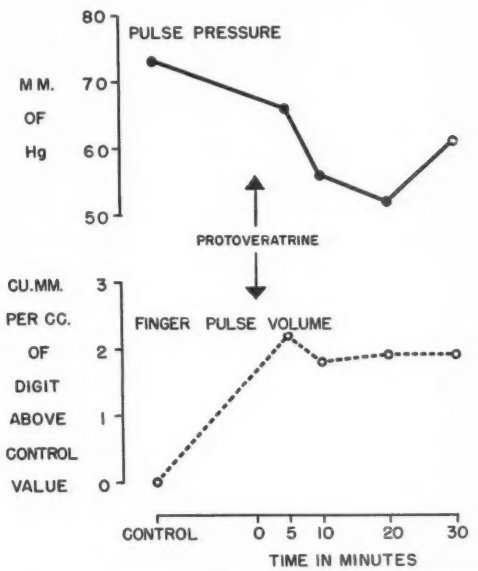

FIG. 5. Change of pulse pressure and finger pulse volume before and after the intravenous injection of protoveratrine. This represents average change of 25 observations on 22 patients. It is noteworthy that the finger pulse volume increases while the pulse pressure decreases.

TABLE 2.—*Change from Control Values at 20 Minutes after Protoveratrine*

	Control	Mean Diff.	% Diff.	S.D. of Diff.	S.E. of Diff.	t	Plus	Minus	0
Systolic b.p.	216	−70.6	−32.6	41.0	7.9	8.9	0	25	0
Diastolic b.p.	134	−43	−32.1	24.9	4.9	8.9	1	24	0
Pulse	78	−19	−24.2	13.0	2.6	7.2	1	24	0
Digital pulse vol. in lt. 5th finger	2.7	+1.9	+71.2	3.1	0.6	3.1	19	5	1
Digital pulse vol. in rt. 2nd toe	1.2	+0.4	+32.2	1.2	0.2	1.6	12	3	10
Finger skin temp.	12.7	+1.9	+14.3	4.6	0.9	2.0	15	9	1
Toe skin temp.	4.9	−.3	−7.1	4.9	1.0	0.4	11	11	3

but the change in the toe skin temperature was insignificant. The change at the time of maximal effect of protoveratrine is summarized in table 2 which gives the change from the control values at 20 minutes. Correlation of the change

TABLE 3.—*Correlation of Change Between Blood Pressure and the Digital Pulse Volume also Digital Skin Temperature Presented 5, 10, 20 and 30 Minutes Following Intravenous Protoveratrine. Finger and Toe Temp. = °F. above Room Temperature*

	5 Min.			10 Min.			20 Min.			30 Min.		
	C*	D†	No‡	C	D	No	C	D	No	C	D	No
Correlation of change with systolic B.P.	4	19	2	3	18	4	5	19	1	5	18	2
Digital pulse volume in (left 5th) Finger with diastolic B.P.	3	21	1	3	18	4§	4	20	1	6	17	2
with systolic B.P.	4	12	9	4	11	10	3	12	10	4	16	5
Digital pulse volume in toe (right 2nd.) with diastolic B.P.	3	13	9	4	11	10	3	12	10	4	16	5
with systolic B.P.	7	17	1	7	18		9	15	1	9	16	
Finger skin temp. diastolic B.P.	8	17		7	18		8	16	1	8	17	
with systolic B.P.	18	5	2	17	7	1	11	11	3	14	9	2
Toe skin temp with diastolic B.P.	18	6	1	17	7	1	10	12	3	13	10	2

* C or concord indicates both change in the same direction.
† D or discord indicates both change in the opposite direction.
‡ No—No change indicated one or both values remain the same.
§ A box to illustrate the changes noted in diastolic blood pressure and digital pulse volume at 10 minutes.

Digital	−	1	0	3	C—3
Pulse	0	0	0	4	D—18
Volume	+	0	0	17	No—4
		+	0	−	

Diastolic B.P.

of blood pressure with digital pulse volume and digital skin temperature was calculated and found not to be significant in any of the combinations recorded in table 3 at 20 minutes. In contrast the calculations for the correlation coefficient of the change between systolic and diastolic blood pressure were found to be significant at 20 and 30 minutes.

DISCUSSION

The above observations support the concept that "vasodilatation" as measured by digital pulse volume and digital skin temperature does occur in most patients during the hypotension induced by protoveratrine. The fact that the pulse volume increased in the finger at the time when the pulse pressure decreased (fig. 5) makes the change more significant, since the expected change in finger pulse volume with a decrease in pulse pressure would be a decrease in finger pulse volume. Comparison of these observations with the hemodynamic effect of protoveratrine after an intravenous injection indicates that the increase in pulse volume in the digit is occurring at a time when the cardiac output usually falls and reaches a minimum at 15 to 30 minutes.[5] These observations suggest that either a decrease in cardiac output or dilatation of some of the arterioles or both could account for the precipitous fall of the blood pressure following the intravenous injection of protoveratrine. However, multiple factors are at work simultaneously and this makes it impossible to attribute the change in blood pressure to one factor. Bradycardia of an important degree is occurring when the blood pressure decreases and when the cardiac output usually falls.[5] The individual variation in the changes in cardiac output and "vasodilatation" may account for the fact that certain patients have more symptoms suggesting a decrease in cardiac output (weakness and giddiness) than other patients during the full effect of protoveratrine.[15]

The evidence for greater "vasodilatation" of the hands compared with the feet is to be noted and resembles the response of normal subjects to reflex "vasodilatation" induced by warming the body.[16] Less evidence of arteriolar dilatation of the feet compared with the hands leads to the speculation that this may account for the lack of postural hypotension from protoveratrine. Change in pulsation or skin temperature of the digits does not indicate what is happening in the rest of the body so that generalizations are not possible. The observation, suggesting greater "vasodilatation" in the

ands, however, is in accord with the clinical bservation of greater warmth and sweating ver the upper portion of the body after proto- eratrine, particularly the throat, chest, and pigastrium compared with the lower portion f the body.[15] The changes after protoveratrine re in contrast to changes from hexamethonium vhich apparently produces a much greater in- rease in digital skin temperature of the foot han of the hand.[10, 11] Hexamethonium is known to produce postural hypotension.[10]

The response to protoveratrine is appreci- ably less than the response to heating the body, particularly in regard to change in skin temperature. The further increase in digital pulsation after the application of body heat, which is usually considered to be reflex in nature, was greater in the finger than in the toe (fig. 3) and this resembled the change after protoveratrine. The greater "reflex" change in the finger compared with the toe both after protoveratrine and the application of body heat is similar to the greater and more rapid increase of finger skin temperature noted by Pickering and Hess in normal adults.[16] They also demonstrated that only part of the "vaso- constrictor tone" of the feet could be abolished reflexly by warming the body, since nerve block of the foot resulted in an increase in skin tem- perature comparable with the rise in finger skin temperature after the application of body heat.

This study does not determine whether the patient develops tolerance or has an altered response to protoveratrine after several months' administration of the drug. Three patients had these studies repeated after six months of protoveratrine administered orally. Two pa- tients had less and one had greater evidence of "vasodilatation" at the time of the second intravenous injection. In the patients who have been observed clinically it has been difficult to distinguish between a decreased response to the drug and progression of the hypertensive dis- ease.[15]

There was considerable variation in the re- sponse of digital pulsation and digital skin temperature of the individual patients in this study. This is demonstrated in the statistical analysis of the data by the standard deviation of the difference being greater than the mean difference in the case of digital pulse volume and digital skin temperature. This indicates that some patients have much more arteriolar dilatation in the extremities from the drug than other patients. The observation that the cardiac output frequently falls after intravenous proto- veratrine indicates that the change in arteriole size is not the only factor which predisposes to a fall in blood pressure.

Conclusions

1. The fall in blood pressure and heart rate in hypertensive patients after intravenous protoveratrine were associated with an increase in digital pulse volume in most patients and the average increase for the group was demon- strated to be significant for the finger.

2. The increase in digital pulse volume was greater in the hand than in the foot.

3. A small increase in digital skin tempera- ture of the finger was observed but no sig- nificant change was noted in the toe.

4. The increase in both pulse volume and skin temperature had a wide range for different individuals and did not occur in all patients.

5. "Vasodilatation" as measured in this study is not the only factor having to do with the decrease in blood pressure since it did not occur in all patients.

Summario in Interlingua

Le cambiamento in le volumine del pulso e in le temperatura del derma del digitos del mano esseva observate in 25 studios post administrationes intravenose de protoveratrina. Esseva notate un significative augmento median del volumine pulsal, sed le differentia inter valores maximal e minimal esseva grande. In le digitos del pede le cambiamento del volumine pulsal non esseva significative. Quanto al temperatura, un leve augmento esseva notate in le derma del digitos del mano. "Vasodilatation" del mano e del pede non occurreva in omne patientes e consequente- mente non esseva le sol factor responsabile pro le reduction del pression sanguinee.

Acknowledgment

We are indebted to Dr. F. A. Simeone for assistance and guidance in the planning of this study. We are also indebted to Drs. Jane Worcester and Mandel Cohen for assistance in the statistical calculations and their interpretation.

Dr. Timothy Counihan, Dr. Buford Hall, Dr. William Thompson, Dr. J. J. Cranley and Dr. J. J. Buchanan were associated with this study. Mrs. Olita Ruza gave technical assistance.

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Cardiac Output and Central Volume as Determined by Dye Dilution Curves

Resting Values in Normal Subjects and Patients With Cardiovascular Disease

By Albert A. Kattus, M.D., Arthur U. Rivin, M.D., Aaron Cohen, M.D. and Gilbert S. Sofio, M.D.

Dye dilution curves determined by the method of Hamilton have been obtained from a series of normal subjects and from a group of patients with various types of cardiovascular disorders. Cardiac indices calculated from these curves revealed expected values. Central volume, believed to be an index of pulmonary blood volume, was calculated from the slopes of the down strokes of the curves. Central volume indices in normal subjects averaged 0.590 liters. Central volume in patients with heart disease was frequently normal or less than normal. Only cor pulmonale patients with high output had central volumes significantly greater than normal.

KNOWLEDGE of the volume of blood in the lungs and the manner in which this volume is altered in various clinical and environmental conditions might be expected to aid in understanding the mechanisms of cardiac dyspnea, pulmonary edema and the redistribution of the blood volume which is believed to occur in congestive heart failure.[1]

A new approach to the indirect determination of the pulmonary blood volume was suggested by Newman and his associates.[2] In 1951, these investigators published a theoretical analysis of dye-dilution curves obtained by the Hamilton single injection technique. They showed that from the slope of the downstroke of the semilogarithmically plotted arterial dye concentration curve one could calculate the volume of the largest mixing chamber traversed by the dye as it traveled from the point of injection in a peripheral vein to the sampling point in a peripheral artery. Newman called the volume calculated from the slope, the "central volume," and postulated that it was identical with or closely related to the pulmonary blood volume. Subsequently, Pearce, Newman, and their associates published supporting evidence for this contention derived from experiments on dogs.[3]

Previous indirect methods for measuring pulmonary blood volume have employed the formula of Stewart[4] which was subsequently modified by Hamilton.[5] With this method, also based on the dye dilution technique, the intrathoracic blood volume is calculated by multiplying the cardiac output by the mean circulation time. Pulmonary blood volume is then obtained by subtracting assumed or calculated values for the volume of blood in the heart and great vessels from the intrathoracic blood volume.

Central volume, on the other hand, is an index of pulmonary blood volume, which is probably independent of the volume of blood in the heart and great vessels, provided that the volume of blood in the right or left chambers of the heart does not equal or exceed the pulmonary blood volume.

It seemed to us desirable to determine the central volume in normal subjects and in a series of patients with various cardiovascular abnormalities in order to ascertain the range of normal values and to note to what extent the abnormal subjects vary from the normal.

Resting, single-injection dye-dilution curves were, therefore, obtained from a group of

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This work was supported in part by a grant from the International Minerals and Chemical Corporation.

normal subjects and from a series of patients with a variety of cardiovascular abnormalities. Cardiac output was calculated from the areas of the curves. Central volume was calculated from the down-slopes of the curves and blood volume was determined from venous blood samples drawn 10 minutes after the dye injection. These values are reported together with certain relationships between them which may be of interest.

Methods and Materials

Normal subjects were healthy, young laboratory and professional personnel. There were only two females in this group. Patients were selected from the wards of the United States Veterans Administration Hospital, Los Angeles, California. All were classified as to functional capacity according to Nomenclature and Criteria for the Classification of Heart Disease of the New York Heart Association.

All subjects were studied in the supine position in the postabsorptive state in the morning after at least 30 minutes rest in the bed on which the test was done. Evans blue dye (T-1824) was injected into an antecubital vein as rapidly as possible through an 18-gauge needle. The time required for the injection was less than one second. The amount of dye injected ranged between six and nine mg. accurately determined by weighing the syringe before and after injection. Arterial samples were obtained through a 17-gauge needle inserted into a procainized brachial artery on the opposite side from the injection. The arterial blood was led through a 20 to 25 cm. length of plastic tubing (3 mm. internal diameter) to a rotating collecting device similar to the one illustrated in Newman's paper. The device was rotated at such speeds that samples were collected over a span of 1.5 to two seconds. Samples ranged in size between one and three ml.

The blood samples were allowed to clot and the tubes were centrifuged. The serum was then transferred to micro cells and the optical density read at a wave length of 620 Å in a Beckman Model B spectrophotometer. The patients' undyed serum was used as the blank. Standard curves were made up in serum, but a fresh standard curve was not made for each patient since curves made up in numerous patients' sera at the beginning of the study showed no deviation from the original standard curve.

The dye concentration curve was then plotted against time on semilogarithmic paper. The straight line down-stroke established prior to the appearance of recirculating dye was extrapolated through at least one cycle of the graph paper. Cardiac output was calculated from the area under the curve as described by Hamilton,[6] and central volume from the cardiac output and the slope of the down-stroke as described by Newman.[2]

Ten minutes after the dye injection a sample o venous blood was drawn for the determination o the blood volume.

Results

The data are presented in table 1 and i graphic form in fig. 1. Cardiac output, centra volume, and blood volume are expressed bot as absolute values and as their respectiv indices, i.e., by dividing the actual values b the surface area of the subject in squar meters.

The ratio, $\frac{cardiac\ output}{blood\ volume} \times 100$, gives tha per cent of the total blood volume which i pumped by the heart in one minute. Lewis an coworkers[7] have recently shown that the norma resting individual has a cardiac output pe minute about equal to his total blood volume Thus if $\frac{CO}{BV} \times 100$ were equal to 100 per cen this is what one would expect of a normal resting individual. If this value were significantly greater than 100 then one would suspect that the cardiac output had been increased over normal perhaps by anxiety or some abnormality of the circulation. Values significantly less than 100 would suggest low cardiac output such as might be seen in cardiac failure or some abnormal depression of the circulation.

The ratio $\frac{central\ volume}{blood\ volume} \times 100$ gives the per cent of the total blood volume which comprises the central volume.

Blood volume per kilogram of body weight is given because numerous other authors have used this method of reference.

In Normal Subjects. In normal subjects cardiac index averaged 3.48 liters per minute. Central volume averaged 1.133 liters with an index of 0.590 liters. It should be noted that the lowest values for central volume index, 0.374 liters and 0.291 liters were found in the only two females in the group. The central volume averaged 20.2 per cent of the total blood volume with a range of 13.5 per cen to 32.8 per cent.

In Patients With Mitral Stenosis. In this group all subjects had what appeared to b pure mitral stenosis without clinical evidenc

TABLE 1.—*Cardiac Output, Central Volume, Blood Volume and their Respective Indices Along with Some Interrelationships of Interest in 9 Normal Subjects and 45 Patients with Cardiac Disease.*

Subject	Age	CO	CI	$\frac{CO}{BV} \cdot 100$	CV	CVI	$\frac{CV}{BV} \cdot 100$	BV	BVI	$\frac{BV}{Kg}$	Class	Remarks
Normal												
				%			%					
D. S.	30	9.02	4.93	127	1.270	.690	17.9	7.09	3.88	107		
... M. ♀	34	5.44	3.70	143	.550	.374	14.5	3.80	2.58	76		
W. F.	31	7.72	3.62	135	.906	.425	15.9	5.70	2.68	64.8		
... R.	29	6.44	3.42	114	1.420	.755	25.2	5.62	3.00	76		
... K.	35	6.80	3.40	119	1.380	.696	24.0	5.70	2.88	65		
... M.	28	6.65	3.36	115	.961	.485	16.7	5.75	2.80	67.3		
M. O. ♀	36	5.44	3.36	155	.471	.291	13.5	3.50	2.16	58.8		
G. S.	30	5.90	3.10	102	1.250	.654	21.7	5.77	3.02	84.8		
J. S.	28	4.80	2.40	83	1.890	.940	32.8	5.77	2.88	67.9		
Mean	31	6.47	3.48	121	1.133	.590	20.2	5.41	2.98	74.2		
Mitral Stenosis												
F. M.	39	6.18	3.43	107.3	1.070	.596	18.6	5.76	3.20	88.1	II	
M. C.	32	6.10	3.26	90.4	.480	.257	7.1	6.75	3.61	99.1	II	Post-commissurotomy
L. W.	35	5.70	3.00	132.6	.550	.289	12.8	4.30	2.26	54.1	II	
R. W.	36	6.69	2.99	103.4	1.370	.612	21.2	6.47	2.89	71.1	II	Post-commissurotomy
N. D. ♀	40	3.82	2.12	97.0	.498	.277	12.6	3.94	2.19	59.7	II	
T. R.	63	3.29	1.89	57.7	1.320	.759	23.2	5.70	3.28	90.2	III	
C. F.	43	2.61	1.62	51.1	1.070	.664	20.9	5.11	3.17	93.8	III	
R. B.	54	2.17			1.090			5.80			III	Bilateral leg amputations
Mean	43	4.57	2.62	91.7	.931	.493	16.6	5.48	2.99	79.9		
Aortic Stenosis												
W. G.	36	7.94	4.51	164.4	.589	.335	12.2	4.83	2.74	74.6	I	
G. M.	31	5.35	3.15	93.2	.644	.379	11.2	5.73	3.37	88.1	II	
A. L.	59	3.92	2.46	67	1.230	.774	21	5.85	3.68	119	III	
T. S.	54	3.57	2.11	96.2	.440	.260	11.7	3.75	2.22	56.1	I	Occasional blackout
A. O.	61	3.53	1.89	71.3	.677	.362	13.7	4.95	2.65	69.3	III	
Mean	48	4.86	2.82	98.4	.716	.422	13.9	5.02	2.93	81.4		
Cor Pulmonale												
W. A.	58	7.65	4.61	117.7	2.520	1.520	38.8	6.50	3.92	117.3	IV	
J. S.	63	7.30	4.04	105	2.010	1.120	29.1	6.91	3.82	106.5	IV	
E. P.	50	7.10	3.21	77.8	1.100	.502	12.1	9.12	4.16	86.9	III	
J. C.	59	5.05	3.18	88.2	.885	.557	15.4	5.74	3.61	104.0	IV	
R. H.	61	3.10	1.59	67.4	.897	.460	19.5	4.60	2.36	51.6	IV	
Mean	58	6.04	3.33	91.2	1.482	.832	23.0	6.57	3.57	93.3		
Pulmonary Fibrosis												
I. H.	22	6.40	4.21	172.0	.277	.182	7.4	3.72	2.45	74.4		No cardiac failure
Thyrocardiacs												
T. B.	58	11.95	6.83	185	.886	.506	13.7	6.45	3.69	112	III	
I. C.	56	9.86	6.75	140	.890	.610	12.6	7.04	4.82	163	III	
S. C.	78	7.13	4.07	102.1	1.130	.646	16.2	6.98	3.99	107.2	III	
A. C.	25	7.20	3.87	105.9	1.020	.546	14.9	6.80	3.65	94.1	III	
A. J.	53	4.90	2.66	104.0	1.500	.815	32.0	4.70	2.56	64.2	I	
Mean	54	8.21	4.84	127.4	1.085	.625	17.9	6.39	3.74	108.1		

TABLE 1.—*Continued*

Subject	Age	CO	CI	$\frac{CO}{BV}$ .100	CV	CVI	$\frac{CV}{BV}$ .100	BV	BVI	$\frac{BV}{Kg}$	Class	Remarks
Congestive Heart Failure												
Hypertensive												
				%			%					
H. S.	60	6.16	3.29	103.7	1.180	.631	19.9	5.94	3.18	83.7	III	
H. H.	62	4.64	2.58	76.1	.839	.466	13.8	6.10	3.39	89.7	IV	
E. B.	66	4.30	2.44	68.8	.610	.347	9.6	6.34	3.60	91.8	III	
W. B.	58	4.17	2.20	43.6	1.500	.773	15.3	9.80	5.05	116.0	IV	
G. W.	63	2.54	1.31	46.2	.630	.325	11.4	5.50	2.84	69.2	III	
Mean	62	4.36	2.36	67.7	.952	.508	14.0	6.74	3.61	90.1		
Arteriosclerotic Heart Disease												
A. McC.	65	6.28	3.41	117.4	1.18	.641	22.1	5.35	2.91	72.7	III	
W. D.	56	3.47	1.99	91.3	1.18	.678	31.1	3.80	2.18	57.1	III	
M. T.	57	3.60	1.81	40.0	1.68	.850	18.7	9.00	4.55	115.0	IV	
Mean	59	4.45	2.40	82.9	1.35	.723	24.0	6.05	3.21	81.6		
Luetic Aortic Insufficiency												
F. M.	68	6.35	2.95	152.0	.830	.386	19.8	4.17	1.94	43.5	III	
R. B.	58	3.70	2.15	88.3	.683	.397	16.3	4.19	2.44	68.2	III	
Mean	63	5.02	2.55	120.1	.756	.391	18.0	4.18	2.19	55.8		
Miscellaneous												
W. H.	65	3.72	2.11	75.3	.713	.405	14.4	4.94	2.81	87	IV	Coarct. aorta
T. W.	45	3.88	1.92	60.8	1.850	.915	29.0	6.39	3.15	73.5	III	Idiopath. myocard.
M. L.	51	2.70	1.44	38.8	1.660	.883	23.8	6.96	3.70	106.0	IV	Mitral insuf.
H. W.	38	5.75	2.93	118.8	1.270	.648	26.2	4.84	2.47	60.9		Apical systolic m., unknown cause. No card. sympts.
H. Sk.	32	6.00	2.75	116.5	1.500	.688	29.2	5.15	2.36	55.4		Aneurysm pulmon. art., asymptomatic.
H. Sp.	28	5.70	2.75	69.5	1.360	.657	16.6	8.20	3.96	96.0		Constrict. pericard. Mild edema.
A. P.	65	4.79	2.63	65.6	.866	.476	11.9	7.30	4.01	100.9		TBC pericard. effusion. Mild tamponade.
C. B.	55	4.94	2.59	111.3	.661	.346	14.9	4.44	2.32	54.9		Complete heart block, pulse 27.
C. H.	58	5.15	2.49	69.6	1.415	.684	19.1	7.40	3.57	78.3		Polycythemia vera. No card. dis.
F. A.	57	3.97	2.46	100.2	.345	.214	8.7	3.96	2.46	66		Complete heart block, pulse 42.
T. G.	47	3.36	1.93	81.0	.467	.268	11.2	4.15	2.38	52.8		Malig. hypertens. No failure.

CO = Cardiac output, liters per minute.
CI = Cardiac index, liters per minute per square meters, body surface area.
CV = Central volume, liters.
CVI = Central volume index, liters per square meters, body surface area.
BV = Blood volume, liters.
BVI = Blood volume index, liters per square meters, body surface area.
$\frac{BV}{Kg}$ = Blood volume in cc. per Kg. body weight.

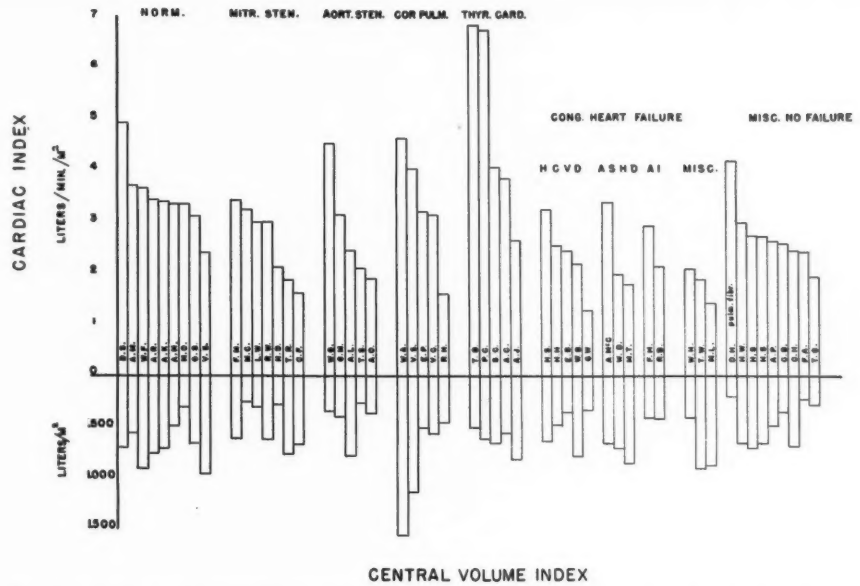

FIG. 1. Cardiac index plotted upward from the base line and central volume index plotted downward from the base line. Clinical categories and individual patients are arranged in same order as in table 1 except for the patient with the pulmonary fibrosis who has been plotted in the miscellaneous no heart failure group.

of significant mitral insufficiency. All but there of them eventually had mitral commissurotomies. Patients M. C. and R. W. were studied only postoperatively three weeks after mitral commissurotomy. At the time of study, rumbling presystolic apical murmurs could still be heard in both of them. Patients R. B. and T. R. were not subjected to operation because of age, and N. D. refused surgery.

Cardiac outputs and indices in this group were generally lower than in the normal subjects, as might be expected. However, some patients did have cardiac indices within normal limits. Central volumes and indices tended to be considerably smaller than normal particularly in patients in class II. The larger central volumes seemed to be in patients in class III. However, F. M. is an exception and did not appear to be different clinically from A. W. who had a small central volume. In the two postoperative patients there were widely divergent central volume indices, 0.257 liters in M. C. and 0.612 liters in R. W. Patient M. C. had had long standing congestive failure prior to surgery and had been greatly relieved by the operation. R. W. had had comparatively mild symptoms and had been able to carry on his work as a school teacher.

In Patients With Aortic Stenosis. In this group cardiac indices were generally low except for W. G. who had a high cardiac output, and G. M. whose output was normal. Central volumes were strikingly small except for A. L. who was in congestive heart failure, and therefore in class III. The other class III patient, A. O., was disabled by angina pectoris but not by congestive failure. In this small series the central volume averaged only 13.9 per cent of the total blood volume.

In Patients With Cor Pulmonale. There were two patients with high cardiac indices in this group and both of these had large central volumes. Two patients had normal cardiac indices and both of these had central volumes in the normal range. One patient had low cardiac index, and his central volume was low. This is the only group in which central volume appeared to be directly related to cardiac output.

In Patients With Pulmonary Fibrosis. The only patient in this group, a 22 year old man, developed cyanosis and clubbing of the fingers following an attack of "virus pneumonia" two years prior to his study. Chest x-ray films showed a diffuse reticular pattern, and lung biopsy revealed marked interstitial fibrosis. Pulmonary ventilation was only mildly reduced. The cardiac index was high and the central volume was 0.277 liters, the smallest central volume found in the entire series of patients.

In Thyrocardiac Patients. Four of these five patients had the circulatory pattern expected in congestive failure due to thyrotoxicosis. The features were high cardiac index and large blood volume. The central volumes were remarkably uniform in this group, falling in the normal range. Because of the expanded blood volumes in this series, central volume comprised a smaller than normal percentage of the total blood volume. Although patient A. J. was mildly thyrotoxic by the usual clinical tests, he did not have the circulatory manifestations of this disease.

In Patients With Congestive Heart Failure. All of the patients in this group had congestive heart failure and were, therefore, in class III or class IV. All of them had clinical edema and all required digitalis, low salt diets, and regular administration of mercurial diuretic drugs. The group is divided into four subgroups; patients with hypertensive heart disease, arteriosclerotic heart disease, syphilitic aortic insufficiency, and a miscellaneous group comprised of: W. H., a man of 65 with coarctation of the aorta, T. W., a 45 year old man with idiopathic myocarditis, and M. L., a man 51 years old, with very marked mitral insufficiency due to ruptured chordae tendineae.

In Congestive Heart Failure Due to Hypertensive Heart Disease. Patients in this group had cardiac indices ranging from normal to very low. Central volumes were in the range of normal in three of the subjects and small in two of them. Central volume did not appear to be related to the cardiac output or to the blood volume.

In Congestive Heart Failure Due to Arteriosclerotic Heart Disease. These three patients all had large central volumes despite low cardiac indices in two and normal cardiac index in one. Blood volumes varied from small to large.

In Congestive Heart Failure Due to Syphilitic Aortic Insufficiency. These two patients had almost identical central volumes despite rather wide variations in cardiac index and blood volume.

In Miscellaneous Congestive Heart Failure. All three of these had very low cardiac indices. The patient with the coarctation had a small central volume while the one with myocarditis and the other with mitral insufficiency had large central volumes.

In Patients With Various Forms of Heart Disease But Without Heart Failure. In this group it is interesting to note that four of the patients had central volume indices ranging from 0.648 liters to 0.688 liters, values which are in the range of most of our normal males. These patients all felt well and had no limitation of their activities. One of these, H. Sp., had constrictive pericarditis which had produced enlargement of the liver and mild ankle edema but had not interfered greatly with his vigorous life. None of these four patients had dyspnea.

A comparison of the patient with constrictive pericarditis and the patient with pericardial effusion (A. P.) reveals that they had similar cardiac indices and similar blood volumes. Both had markedly elevated venous pressures. Yet, the central volumes showed marked differences, the pericardial effusion patient having a central volume index of 0.476 liters as opposed to the constrictive pericarditis patient with a central volume index of 0.657 liters. Both patients with complete heart block had small central volumes. The patient with malignant hypertension died of a cerebral hemorrhage a few days after our test.

Discussion

Early efforts to measure the pulmonary blood volume directly were summarized by Drinker, Churchill and Ferry in 1926.[8] They cite the work of Spehl and his associates dating back to 1881. These investigators abruptly ligated the vessels leading into and out of the

heart in rabbits during various phases of respiration both at sea level and at 3,000 meters altitude. They found that the rabbit lungs contained 8 to 9 per cent of the total blood volume at the end of inspiration, 5 to 6 per cent of the total blood volume at the end of expiration. At high altitude the lungs contained slightly more blood. Similar experiments were performed on dogs by Plumier[9] who found pulmonary blood volume to be about 10 per cent of the total blood volume.

Kuno[10] employed the dog heart-lung preparation ligating both lung hila simultaneously. He found values of pulmonary blood volume ranging from 9 per cent to 20 per cent of the total blood volume. In this series the pulmonary blood volume increased as the cardiac output increased. In two dogs in which pulmonary edema was induced the amount of blood in the lungs was 26.2 per cent and 23.4 per cent of the total blood volume.

Indirect methods for measurement of pulmonary blood volume were introduced by Stewart[4] in 1921 when he published his formula for calculating pulmonary blood volume by multiplying cardiac output by the mean circuation time through the lungs. He believed that le could obtain the mean pulmonary circulation time by making minor corrections in the lobserved circulation time. He believed that at east in small animals the major part of the circulation time was spent in traversing the lungs. Employing his method in dogs he obtained pulmonary blood volumes of about 20 per cent of the total blood volume.

Stewart's method was subsequently modified by Hamilton and his associates[5] who first employed a single rapid injection of dye and calculated cardiac output from the extrapolated curves of the dye concentration during its first circulation. Hamilton pointed out that in the human the volume calculated from the cardiac output multiplied by the mean circulation time really includes the blood in the heart, lungs, and great vessels leading to and from the heart.

A number of investigators in recent years have employed the Stewart-Hamilton formula to obtain the intrathoracic blood volume. Among these have been Ebert, Borden, Wells and Wilson,[11] Lagerlöf, Werko, Bucht and Holmgren;[12] Kopelman and Lee;[13] and Doyle, Wilson, Lepine and Warren;[14] all of whom injected the dye through a catheter into the right heart or pulmonary artery.

The data from the Ebert group are almost identical with ours for the normal subjects. However, they found slightly higher than normal values for intrathoracic blood volume in mitral stenosis and considerably higher values in left ventricular failure. Kopelman and Lee found higher values for intrathoracic blood volume when dye was injected through an antecubital vein than they did when injection was made through a catheter. Their average normal values were considerably higher than ours. In mitral stenosis they found that intrathoracic blood volume was not significantly increased and there was very little difference between the values in compensated and decompensated individuals. In left ventricular failure intrathoracic blood volume was considerably increased over normal and with compensation it decreased.

Lagerlöf and his coworkers estimated the volume of blood in the heart from the size of the x-ray film silhouette and, using an estimated volume of blood in the aorta and large arteries, subtracted these from the intrathoracic blood volume to obtain the pulmonary blood volume. With this method the mean pulmonary blood volume index in seven normal subjects was 597 cc. Patients with hypertension, mitral stenosis and pulmonary disease had pulmonary blood volumes which were not significantly different from normal nor was there any significant difference between compensated and uncompensated cardiac patients.

In the study of Doyle and associates mean intrathoracic blood volume index was 634 cc. in normal subjects and 892 cc. in patients with congestive heart failure. These investigators found a significant difference between patients with mitral stenosis whose intrathoracic blood volumes averaged 28 per cent of the total blood volume and patients with tricuspid insufficiency whose intrathoracic blood volumes averaged 19 per cent of the total blood volume.

Nylin and Celander[15] used radioactive phosphorus labeled red blood cells to obtain dilution

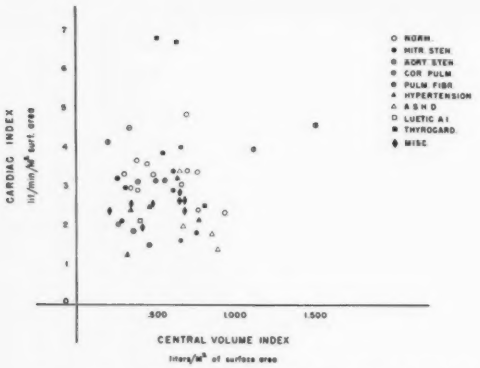

FIG. 2. Scatter graph in which cardiac index is plotted against central volume index. No correlation between the two is shown.

curves. Using their own modification of the Stewart-Hamilton formula they obtained values for intrathoracic blood volume amounting to about 33 per cent of the total blood volume.

It is difficult to account for the strikingly good agreement between our data for central volume in normal subjects and the data obtained by Borden and coworkers, Lagerlöf and associates and Doyle and colleagues for normal subjects. The volumes determined by Borden and associates and by Doyle and his coworkers include blood in the left heart and major arteries while the volumes calculated by Lagerlöf do not. Our data, of course, were calculated in an entirely different manner. Yet, average values for pulmonary blood volumes in all four groups of normal subjects are surprisingly close.

In the groups with disease, wide discrepancies between our data and those of the other investigators are noted. The others have found pulmonary blood volumes equal to or greater than normal in patients with mitral disease. We have found generally smaller than normal central volumes in patients with valvular heart disease. The degree of compensation did not seem to be a factor in determining whether this volume was small or large. There did not appear to be significant differences between patients with mitral stenosis, aortic stenosis, or aortic insufficiency.

While Borden and colleagues, Kopelman and Lee, and Doyle and associates found increased intrathoracic blood volumes in congestive heart failure, Lagerlöf and his co-workers found no significant increase in pulmonary blood volume in patients with heart failure. Most of our patients with congestive failure had central volumes within the normal range. However, those with arteriosclerotic heart disease tended to have higher volumes than those with hypertensive or with valvular disease.

Patients with high cardiac output cor pulmonale had the highest central volumes in this series, while the patient with pulmonary fibrosis and no cardiac failure had the smallest central volume in the series.

The thyrocardiacs, despite the high cardiac outputs, had central volumes within the range of normal. No consistent pattern could be discovered among those patients in the miscellaneous group who were studied.

That the size of the central volume is not related to the cardiac output is illustrated in the scatter graph (fig. 2) which plots central volume index against cardiac index.

Thus the pulmonary blood volume as estimated from the slope of the dye-dilution washout curves seems to vary considerably among normal subjects and patients with a variety of cardiovascular diseases with no sharp distinctions between clinical categories. It may be that the size of this volume is governed by factors as yet undiscovered.

SUMMARY

1. Single injection dye-dilution curves have been obtained on a series of nine normal subjects and 45 patients with a variety of cardiovascular abnormalities.

2. Cardiac indices were determined from the areas of the curves and central volume indices from the slopes of the semilogarithmically plotted downstrokes of the curves. Central volume is believed to be identical with or closely related to pulmonary blood volume.

3. Cardiac indices in this series revealed expected values.

4. Central volume indices in normal subjects averaged 0.590 liters.

5. Central volume indices in patients with valvular heart disease and hypertensive con-

gestive heart failure may be smaller than normal.

6. Central volume indices in numerous patients with cardiovascular abnormalities were within the range of normal values.

7. The largest central volume indices were found in patients with high cardiac output cor pulmonale while the smallest central volume index was in a patient with pulmonary fibrosis.

Summario in Interlingua

1. Curvas del dilution de colorantes post non-repetite injectiones esseva obtenite ab un serie de nove subjectos normal e de 45 patientes con un varietate de anormalitates cardiovascular.

2. Indices cardiac esseva determinate super le base del areas del curvas. Indices de volumine central esseva determinate super le base del descenditas del curvas in presentation semilogarithmic. Nos ha rationes a creder que le volumine central es identic, o strictemente relationate, con le volumine de sanguine pulmonar.

3. In le serie hic presentate le indices cardiac esseva conforme al valores expectate.

4. In individuos normal le valor median del volumine central esseva 0,590 litros.

5. In patientes con morbos cardiac valvular e hypertensive insufficientia congestive del corde le indices del volumine central pote esser infra le norma.

6. In multe patientes con anormalitates cardiovascular le indices del volumine central esseva infra le limites normal.

7. Le plus alte indices de volumine central esseva trovate in patientes con corde pulmonar e alte rendimento cardiac. Le plus basse indice de volumine central esseva illo de un patiente con fibrosis pulmonar.

Acknowledgments

The technical assistance of Mrs. Mabel Pearson and Miss Thelma Dailey is gratefully acknowledged.

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Primary Hemangioendotheliosarcoma of Heart, Diagnosed by Angiocardiography

Review of the Literature and Report of a Case

By TSUNG O. CHENG, M.D., AND DON C. SUTTON, M.D.

Primary malignant tumors of the heart are rare and are seldom recognized before death. This paper reports a case of primary hemangioendotheliosarcoma of the right atrium of the heart, which was diagnosed clinically by angiocardiography. A brief review of the literature is also presented. No reports are to be found in the literature of the antemortem diagnoses of a primary hemangioendotheliosarcoma of the heart by angiocardiography. Autopsy findings are included.

WHEREAS a considerable number of tumors of the heart have been reported in the literature, they are still a relatively rare occurrence. Primary cardiac malignancies are rarer still, their ratio to metastatic tumors being 1 to 16,[1] and of this group the malignant hemangioendothelioma is among the least common.[2] Recognition of cardiac tumors during life, especially in the primary form, is extremely difficult. Up to the present time the diagnosis of primary malignant tumor of the heart has been made ante mortem in only six instances; in all the tumors were sarcomas.[3-7] In no case was angiocardiography employed, although the latter procedure had been successfully employed in one case of myxoma[5] and other intra- and extracardiac tumor masses.[8, 9]

Only seven[1, 2, 4] cases of primary hemangioendotheliosarcomas of the heart have been reported; our case will be the eighth. It is of interest to note that the case we are presenting is the first case in which the correct diagnosis was suggested ante mortem by angiocardiography.

CASE REPORT

A 45 year old Negro man entered the Cook County Hospital on Feb. 11, 1954, complaining of substernal pain, cough and dyspnea of three weeks' duration, and swelling of face and feet of one week's duration. He had been well until three weeks before admission when he rather suddenly developed substernal pain that was aggravated by coughing and deep respiration, and a cough productive of a scanty amount of rusty sputum. On one occasion about half a teaspoonful of bright red blood was coughed up. At about the same time he developed dyspnea which was most pronounced on sitting up and seemed to be relieved by lying down. Progressive swelling of his face and both feet, which appeared one week before hospitalization, was most marked at night.

Physical examination on admission showed the patient to be a well developed, well nourished middle-aged Negro man. He lay comfortably in bed. Temperature was 99 F., blood pressure 100/86, respiration 28 per minute, and pulse 112 per minute and regular. There was slight edema of the lower lip but none of the face. The cervical veins were prominently distended on both sides, more so on inspiration. Examination of the chest revealed a patchy area of bronchial breathing and moist rales below the angle of left scapula. Cardiac dullness extended to the midaxillary line in the sixth intercostal space, and there was some apparent widening of the supracardiac dullness in the supine position. The heart sound were slightly muffled. No murmur or rub was heard. The liver edge was palpable 4 cm. below the right costal margin; it was soft, smooth, and moderately tender. There was no ascites or peripheral edema.

The urine showed a trace of protein and many fine granular casts. The hemoglobin content was 89 per cent, the red cell count 4,900,000, and the leukocyte count 14,600. The nonprotein nitrogen content of the blood was 50 mg. per 100 cc. Sedimentation rate (Wintrobe method) was zero. Blood Kahn test was negative. One blood culture showed no growth. An electrocardiogram revealed a right axis shift and a semivertical electrical position of the heart, with low voltages of all the complexed, inverted T waves in precordial leads V_1, V_2 and V_3 and isoelectric T waves in V_4, V_5 and V_6. The corrected Q-T interval was 0.40 second. Venous pressur

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was 320 mm. saline by the method of Moritz and Tabora. Circulation time was 8 seconds with ether and 30 seconds with magnesium sulfate. X-ray films of chest (fig. 1) revealed gross cardiac enlargement both to left and right, with haziness over left lower chest.

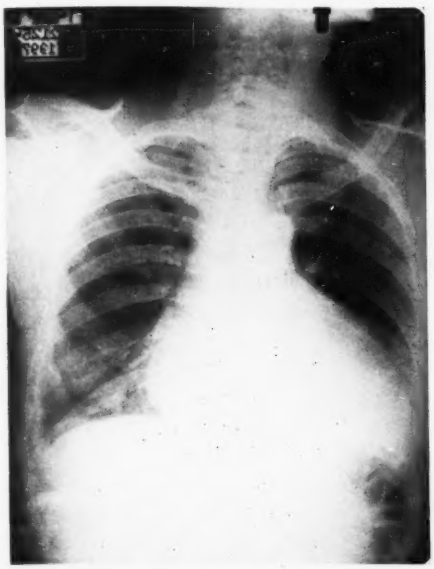
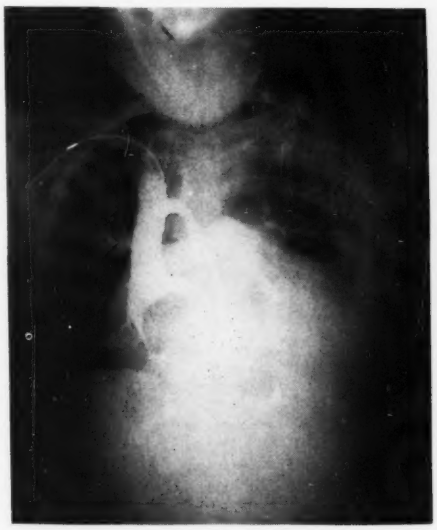


FIG. 1. Roentgenograms of chest. Note the gross enlargement of the heart both to left and right.

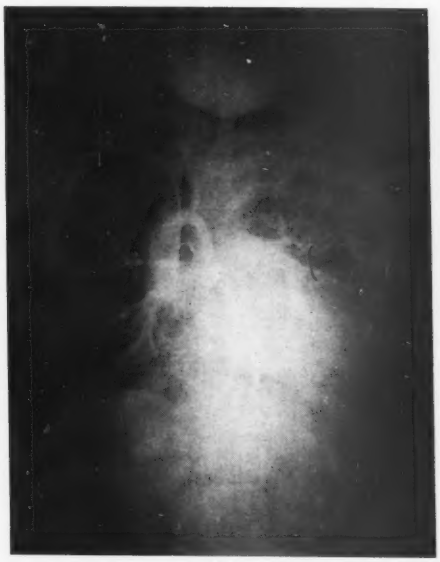
Patient was treated with digitalis, penicillin, tetracycline, Meralluride and Diamox. During his hospital course he was entirely afebrile. On the fourth hospital day, a paradoxic pulse was detected. More prominent venous engorgement was noted in the neck, both upper extremities and the upper chest. On the sixth hospital day pericardiocentesis was performed through the fifth left intercostal space external to the cardiac apex and also through the left xiphocostal angle. Both attempts failed to obtain any fluid. Following this a loud pleural friction rub was heard on the left side, especially around the apex of the heart.

On the eighth hospital day angiocardiography was performed. The films taken four and one-half seconds and six seconds after the dye injection (Urokon sodium, 70 per cent) showed good filling of the azygos vein, superior vena cava and the pulmonary artery. In the enlarged right atrium, a large filling defect which was constant in shape, size, density and position was seen in the films made four and one-half and six seconds after injection of the contrast substance (fig. 2). In view of the angiocardiographic findings along with the clinical course of the patient, a diagnosis of a primary cardiac neoplasm was suggested.

The patient's condition gradually grew worse, his edema became generalized, and the patient finally



A



B

FIG. 2. Angiocardiography. Films selected from serial studies in frontal projection made following intravenous injection of 50 cc. of Urokon sodium (70 per cent). (*A*) At 4.5 seconds. (*B*) At 6 seconds. Between 4.5 and 6.0 seconds following the injection there was good opacification of the superior vena cava, azygos vein, part of the right atrium and the pulmonary artery. The right atrium was enlarged and was the site of a large irregular filling defect, constant on both films.

expired on the thirteenth hospital day, after a total known duration of illness of five weeks.

Necropsy Findings: The pericardial sac contained 50 cc. of hemorrhagic fluid. The heart weighed 700 Gm. The right atrium of the heart was enlarged. Arising from the right atrium was a large cauliflower-shaped hemorrhagic tumor mass which bulged into the pericardial cavity. The tumor extended through the wall of right atrium, arose from the posterolateral aspect of the right atrium, and almost filled the entire right atrium, extending upward into the right atrium and down through the tricuspid valve orifice into the right ventricle (fig. 3). The superior vena cava was almost completely obstructed up to the level of the innominate vein. On cross section the tumor tissue was purplish and hemorrhagic, with whitish specks scattered throughout. The remaining chambers of the heart and the valves were not unusual. The coronary arteries were all patent. Except for a few scattered hemorrhagic areas in the right ventricle, the myocardium was normal. The left pleural cavity contained 100 cc. of bloody fluid and the underlying left lung showed atelectasis. The pleural surfaces of both lungs were covered with many fine, round, purplish hemorrhagic nodules. The liver weighed 2000 Gm., showed severe congestion, and contained one round, slightly umbilicated, purplish tumor nodule.

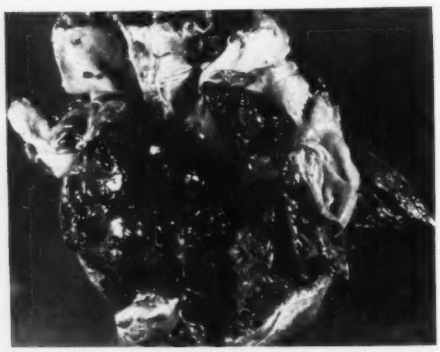
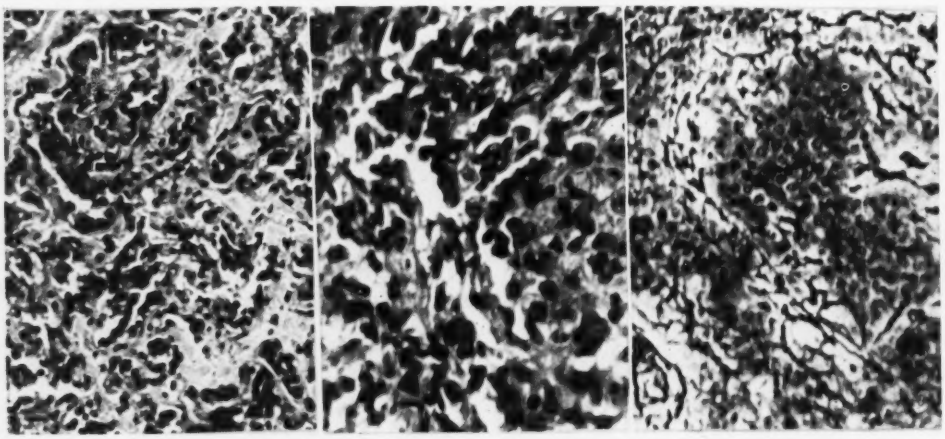


FIG. 3. Interior of right atrium showing the tumor growing down through the tricuspid valve opening into the right ventricle.

Several sections from the primary tumor of the heart showed a considerable pleomorphism. Most of the tumor consisted of various sized, blood-filled spaces, making up what appeared to be poorly formed vascular channels. There were large sinus spaces with marked proliferation of endothelial lining and small thick-walled capillaries about these cavernous vascular spaces filled with blood (fig. 4*A*). The endothelial lining cells varied in shape and size, and had a varying amount of pale eosinophilic cytoplasm and hyperchromatic irregular nuclei which had a fine network of chromatin with a few small and indistinct centric or eccentric nucleoli. Mitotic figures were frequently seen (fig. 4*B*). In other areas the capillaries had distinct thick walls composed of concentrically layered, plump, rounded pericytes (fig. 4*C*). There were also areas of necrosis and hemorrhage. Scattered in the myocardium of the right ventricle were many extensive hemorrhagic infarcts with leukocytic infiltration due to obstruction of the thebesian veins.

The histologic picture of the metastatic nodules in the lungs varied from capillary hemangioendothelioma with pericytomatosis to cavernous hemangioma.



A *B* *C*

FIG. 4. Microscopic appearance of various portions of the tumor showing (*A*) hemangioma, (*B*) hemangioendothelioma, and (*C*) hemangiopericytoma.

The liver showed severe congestion with marked central necrosis, but no fibrosis. The tumor nodule on the surface was a cavernous hemangioma.

Discussion

The case we have presented was that of a 4[illegible] year old man with symptoms of rather sudden onset of severe congestive heart failure due to an obstruction to the inflow of blood from the great veins into the right side of the heart. It was at first thought that the patient might be suffering from tuberculous pericarditis with effusion; but this diagnosis was soon abandoned because of a "dry" pericardiocentesis. Moreover, the sedimentation rate of zero was not entirely consistent with an active tuberculous process. The diagnosis of an "idiopathic" myocarditis was then considered. However, this diagnosis was also believed unlikely because of absence of fever, normal sedimentation rate, lack of tachycardia, a normal Q-T interval in the electrocardiogram, and the atypical clinical course with a predominant picture of unexplained obstruction to the venous inflow. The possibility of an intracardiac tumor, probably a neoplasm, was therefore finally considered. Support of this diagnosis was rendered by angiocardiography, and confirmation was obtained at necropsy.

Tumors of the heart are rare. Metastatic tumors are more common than those of the primary type, and benign tumors are more frequently found than malignant primary growths. Figures based on necropsy material vary considerably. According to Straus and Merliss,[10] the incidence of primary tumor of the heart is 0.0017 per cent. This percentage is probably close to the actual incidence of primary cardiac tumors. Mahaim[11] collected 3[illegible] published cases of primary tumors of the heart from the world literature; of these 87 were malignant. Whorton[3] collected 99 cases of primary malignant tumors of the heart from the literature, to which he added one of his own. In 1951, Prichard[6] in his review brought the total of primary cardiac neoplasms to 416, of which 113 were primary sarcomas. Twenty one more have since been reported,[1, 2, 12-28] bringing the total of reported primary sarcomas of heart to 134.

Primary cardiac sarcomas are more common on the right side, especially the right atrium, in contrast to the benign myxomas which are more often found in the left atrium. According to Whorton,[3] three-fourths of all cases of primary cardiac neoplasms occur between the ages of 20 and 60, the mean being 43 years.

There are no pathognomonic symptoms or signs of primary malignant tumors of the heart. Several authors, particularly Yater,[29] Mahaim,[11] Woll and Vickery,[31] Whorton[3] and Pfeiffer,[30] have discussed this subject at length. In many cases the diagnosis is one of exclusion and is usually only suggested by the peculiar, atypical course of intractable heart failure in a previously healthy individual without obvious cause. Mahaim, cited by Whorton,[3] has pointed out that, "The symptomatology of cardiac sarcoma is dominated by the frequency of its localization in the right auricle. This may give rise to obstruction of the neck veins, edema of the face, upper trunk, upper extremities, and the development of collateral circulation. Uncommonly a cardiac tumor mass in the superior mediastinum may cause a dry cough and very rarely dysphagia. Precordial or chest pain is not uncommon. Auricular sarcomas may take the form of a polypoid lesion that gives rise to a ball-valve action on the tricuspid valve." Gould[32] mentioned respiratory difficulty as a striking feature in a patient with atrial tumor. Grewin[33] stated that a common syndrome in malignant tumor in the heart is cough with hemoptysis, congestion of the veins of the upper part of the body and pericarditis.

Roentgenographic examination can be helpful in diagnosis.[29, 34-39] Electrokymographic or roentgenkymographic studies,[11, 35, 40] tomography,[37] pneumopericardium,[4] and angiocardiography[5, 8, 9, 11, 41] may all help to clarify the diagnosis. In our case serial films made during the period of right atrial opacification showed a large, round filling defect. This presented a regular, constant contour and border in serial films in contrast to the irregular and inconstant border seen in tricuspid insufficiency, the latter being described as the "jet sign" by Dotter, Lukas and Steinberg.[42] Although the antemortem diagnosis of primary

tumors of the heart have been made six times[4, 7, 43-46] previously, our case is the first case of primary cardiac sarcoma which was diagnosed by means of angiocardiography. It seems that, had angiocardiography been available to or used by the previous authors, more cardiac tumors could have been successfully diagnosed definitely during life.

Summary

1. A case of primary hemangioendotheliosarcoma of the heart is reported.

2. The diagnosis was suspected ante mortem on the basis of angiocardiographic demonstration of a filling defect in the right atrium.

3. Certain clinical manifestations are presented which were suggestive, although not diagnostic. The recognition of this rare condition during life is not entirely impossible.

4. This case of primary cardiac sarcoma brings the total recorded to 135. It is the eighth malignant hemangioendothelioma of the heart reported, the second diagnosed during life, and the first demonstrated by angiocardiography.

Summario in Interlingua

1. Es reportate un caso de primari hemangioendotheliosarcoma del corde.

2. Le diagnose esseva previdite ante morte super le base de un demonstration angiocardiographic de un defecto projicite al interior del atrio dextere.

3. Es presentate certe manifestationes clinic que esseva de valor suggestive ben que non diagnostic. Le recognition de iste rar condition morbose durante le vita del patiente non es integremente impossibile.

4. Iste caso de primari sarcoma cardiac avantia le total del casos reportate in le litteratura a 135. Inter istos illo es le octave caso de maligne hemangioendothelioma del corde, le secunde diagnosticate durante le vita del patiente, e le prime demonstrate per angiocardiographia.

Acknowledgment

The authors wish to thank Drs. R. Wallyn and R. Dillon of the Department of Cardiology for their help and suggestions in the performance and interpretation of the angiocardiograms.

We are also greatly indebted to Dr. Hans Popper of the Department of Pathology for permission to use the photographs of the autopsy material.

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CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

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Diagnostic Roentgenology in Congenital Heart Disease

By MARTIN H. WITTENBORG, M.D. AND EDWARD B. D. NEUHAUSER, M.D.

ROENTGENOGRAPHIC and fluoroscopic observations, always important to the patient and physician when heart disease is suspected, gain significance only by correlation with information gained by other methods. Isolation or over-emphasis of roentgenologic observations is as a sentence read out of context. The recognition of a pattern might well be called interpretation. The "coeur en sabot" heart, fondly thought of by many as diagnostic of the tetralogy of Fallot, assumes an entirely different significance in the absence of cyanosis, or in the presence of left ventricular dominance as shown by an electrocardiogram. Should we discard a medical finding because of lack of specificity when, basically, it is the recognition of its relation to the pattern that actually makes it significant?

Certain roentgenographic technics, such as angiocardiography, kymography, and retrograde aortography, have not enjoyed as broad a sphere of usefulness as the heart film or fluoroscopy. The importance of these technics lies in the very specific, though limited, information they yield. At times they constitute the key to the differentiation of one entity from the other. We should not like to argue the question of whether the already assembled or the missing pieces of a jigsaw puzzle are the more important.

THE GROWING HEART

The size, shape, and beat of the heart and its vessels are products of its basic embryologic design and of its load, past and present. Radiologic examination of these features yields information on the structure of the heart and its load. In acquired heart disease of older children or adults, the recognition and interpretation of these changes is a relatively simple process. One assumes that the patient began life with a normal heart already well developed into four chambers, that this was followed by the development of normal left ventricular dominance, and that this pre-existing familiar picture was altered by disease. Whether there be valvular stenosis, insufficiency, or altered extracardiac work load (hypertension, traumatic arteriovenous fistula, and so forth), the heart responds by adding hypertrophy or enlargement to the known pre-existing pattern. Occasionally, one may see diminution in size (Addison's disease), but in all instances of acquired disease (as opposed to congenital malformations) there is an alteration of the normal adult four-chambered heart. Selective chamber enlargement is relatively easily recognized, and criteria are well established.

The course of events in the development of the normal heart is well documented. *In utero*, as at birth, the heart reflects the load of the fetal circulation, resulting in right and left ventricles of comparable size with right and left myocardium of equal thickness. Most normal hearts at birth will measure and weigh approximately the same; in fact, the majority of congenitally defective ones will also show little variation in size in the first few weeks of life. The commonest congenital malformations will normally sustain fetal circulation. If the developmental malformation of the heart grossly

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fails to sustain fetal circulation, intrauterine death intervenes. As a result, most infants begin life with a heart of approximately the same external dimensions and configuration. Only those having primary myocardial disease, aortic atresia, and congenital arteriovenous aneurysms are the exceptions. Thus, roentgenograms will fail to distinguish the normal heart from the majority of hearts having congenital lesions at, or shortly after, birth.

When the lungs become aerated shortly after birth, after the foramen ovale ceases to function, and after the ductus closes, the pulmonary and systemic circulations are separated. The left ventricle gradually hypertrophies, paralleling the increased pressure of the systemic circulation. The left ventricle thus becomes heavier and larger, and thereby the dominant chamber of the heart. Normally, this trend probably persists throughout life, the left ventricle continuing to hypertrophy relatively more than the right until myocardial degenerative changes set in due to impaired circulation, fibrosis, or other factors, or until the load balance is altered by acquired valvular or pulmonary disease. Hypertension in the young adult simply aggravates this trend. It is evident that the size and configuration of the heart, despite a probable plateau in the middle span of life when it is relatively stable, is not static.

Cardiac Size and Mensuration

No simple method of roentgenographic cardiac measurements has yet been devised which has proved to be of practical value in infancy and early childhood. The reasons are fundamental.[1] The standardization of the radiographic technic is too difficult to be a simple clinical procedure. The physiologic variations in size due to respirations within the individual exceed variations of pathologic significance for any given stage of the respiratory cycle. As the average child less than four years old will rarely hold the same degree of inspiration during roentgenologic exposure, this variation becomes critical. The majority of congenital cardiac abnormalities are associated with enlargement of a chamber, which is not readily reflected in a single diameter of the heart, particularly not the transverse diameter. A prime example is the tetralogy of Fallot.

Cardiac Configuration

The shape of the heart is determined not only by its position, component chambers, and content, but by its own elastic resistance or muscle tone.

Criteria for enlargement of a chamber in acquired heart disease are readily available in radiologic texts. This is not true in congenital cardiac disease. In congenital malformations of the heart, development may be so abnormal as to bear no resemblance to the normal adult four-chambered organ. At times, one may be dealing with only one ventricle. Examples of this are a congenitally single ventricle with truncus communis, and tricuspid atresia or severe tetralogy of Fallot, where the substance of the heart is predominantly one ventricle. In none of these is the enlarged ventricle superimposed upon a normal heart or even a normal opposite ventricle. In the tricuspid atresias, the right ventricle is congenitally rudimentary or is completely absent, while in the extreme types of tetralogy of Fallot, the left ventricle may remain essentially infantile in development as a result of the diminished load. In both of these examples the substance of the heart may be so overwhelmingly one ventricle, without a fully developed opposite ventricle, that the ventricular configuration loses its roentgenographic distinguishing characteristics. Thus, the roentgenologic appearance of the heart with these lesions approaches a common form. In this case, there are no universally applicable roentgenologic criteria of left and right ventricular enlargement.

In clinical medicine, one sees a patient more often who has a congenital heart defect which altered the extrauterine load on the heart and, thereby, its normal development. Here again, the usually accepted roentgenographic criteria of selective chamber enlargement are not applicable. In contrast to acquired heart disease, where chamber enlargement alters a pre-existing pattern, the heart fails to develop the adult chamber relationship.

The commonest stumbling block in evaluation of the heart shape in congenital heart disease is the recognition of right-sided enlargement. What part the right ventricle normally plays in forming the right border of the heart in the posteroanterior silhouette on

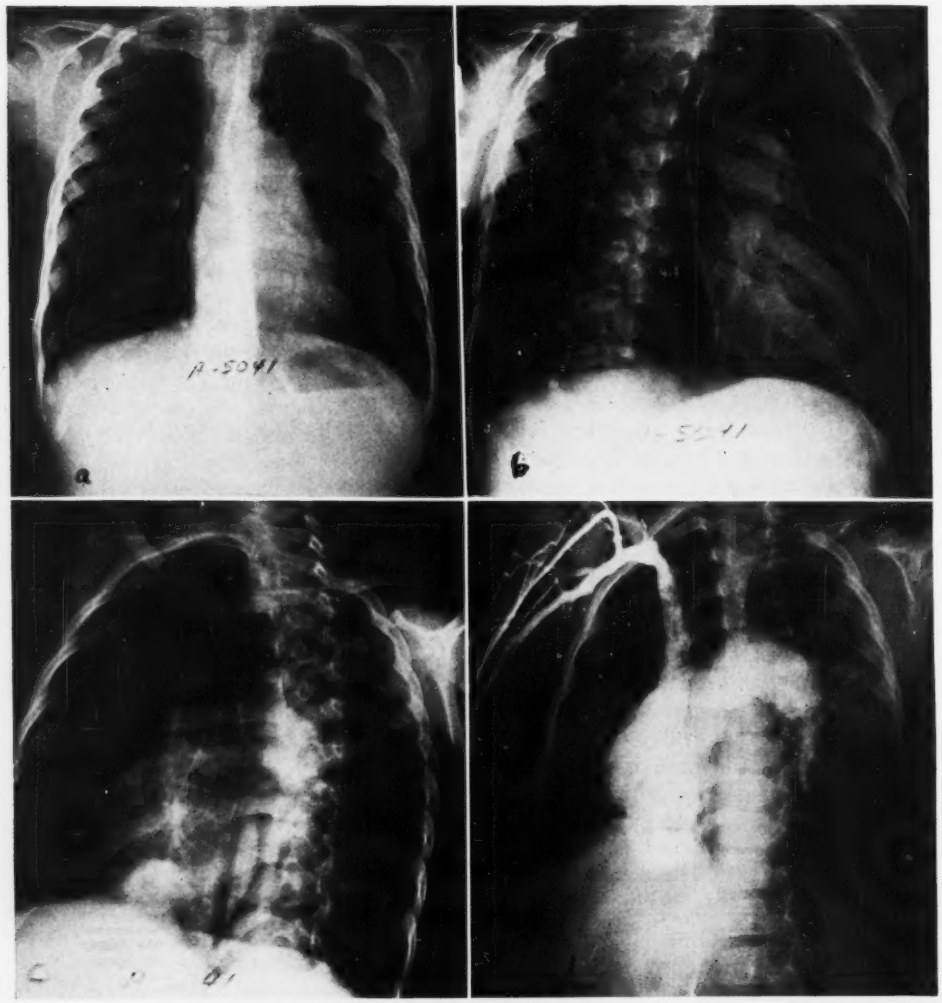


FIG. 1. Right ventricular hypertrophy with only slight chamber enlargement as seen in valvular pulmonic stenosis. Here the left ventricle is of normal size and is not displaced by the right ventricle, which is hypertrophied but only slightly enlarged by external dimension. a. Posteroanterior projection. Note normal transverse diameter with a configuration not specifically abnormal. b. Right anterior oblique projection. There is a slight increase in anterior-posterior dimension. c. Left anterior oblique projection. The slight right ventricular enlargement is recognized by the slight increased convexity of the anterior border and slight upward displacement of the left ventricle, resulting in a poorly defined apex and an almost round shape. d. Left anterior oblique projection with contrast media in right side of heart showing how the right ventricle lies anteriorly and in contact with the diaphragm. Enlargement of this chamber will cause counter-clockwise rotation of the apex in this view.

the roentgenogram has been a controversial subject since the earliest writings on cardiac roentgenology. The effect of selective hypertrophy and enlargement of the right ventricular chamber is now well understood but not widely recognized. Ordinarily, the right ventricle does not add appreciably to the transverse diameter of the heart when it is only slightly

o moderately enlarged. However, it may alter t e contour of the heart in the posteroanterior v ew by elevating the left ventricle in a coun- t rclockwise direction, thus raising the apex c the heart and giving it a rounded appear- a ice. As the increase in size of the right ven- t icle is normally toward front and back, it w ll be demonstrated optimally in the oblique p ojections where the increase in horizontal d mensions becomes obvious in the right a terior oblique, and its alteration of the configuration is most striking in the left a terior oblique, in that the apex is elevated a d poorly defined, and the heart appears almost round (fig. 1).

These changes take place in the presence of a normal left ventricle. If the hypertrophy of the right ventricle is associated with moderate enlargement but is unbalanced by a normal left ventricle, the classic "coeur en sabot" shape results. Here, the left ventricle remains infantile or hypoplastic in development as the right is sharing a large part of the work necessary to sustain the systemic pressure. The small left ventricle is cocked up high as the right ventricle becomes the increasingly dominant chamber (fig. 2).

If the right ventricular enlargement is balanced by a well-developed or enlarged left ventricle, the effect on the cardiac configuration is of the type more familiar in acquired heart disease, as seen in mitral insufficiency with stenosis. The left ventricle is not so readily displaced by the addition of an enlarged right. In this case, right ventricular enlargement is almost immediately reflected by increase in the maximum transverse diameter of the heart, including the right border, with some increased convexity on this side. The forward bulge of the anterior contour of the heart in both obliques, so commonly described in the literature, is recognized under these conditions only when the well-developed or thick left ventricle is no longer readily displaced posteriorly and upward. This type of right ventricular enlargement is seen in the high ventricular septal defect where pulmonary hypertension gradually may add right ventricular enlargement to an already heavy, hard working left ventricle, resulting in a balanced enlargement of the heart (fig. 3). Similar examples, for which there is no place here, may be given for each of the cardiac chambers. Thumb rules of chamber enlargement of acquired heart disease are not generally applicable in many developmental lesions, and, again, the part is evaluated in light of the whole.

Localization of the interventricular notch or measurements of the left anterior oblique dimensions of the heart, based on an estimate of the position of the septum, as recently

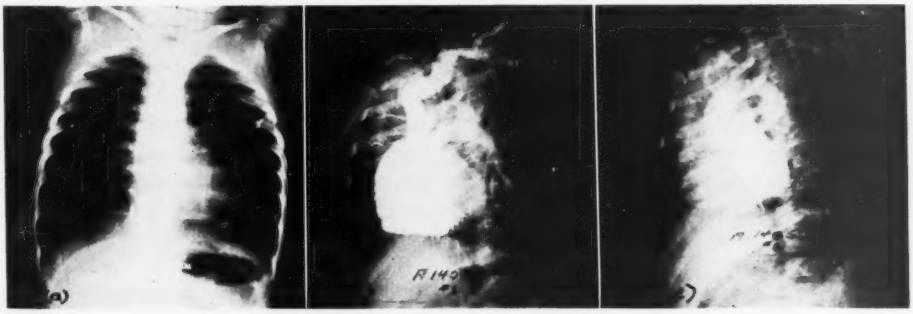


FIG. 2. Right ventricular enlargement as seen in a moderately severe tetralogy in which the right ventricle is the dominant chamber of the heart. a. Posteroanterior projection showing normal transverse diameter but a distinct elevation of the apex of the heart with an almost round right and lower border. b. Left anterior oblique projection with contrast material outlining the right side of the heart. c. Same projection with contrast material outlining the left ventricle. This heart illustrates how the enlarged right ventricle displaces a relatively small nonhypertrophied left ventricle upward in a counter-clockwise rotation. This results in the "coeur en sabot" configuration in the posteroanterior projection and a round heart in the left anterior oblique projection.

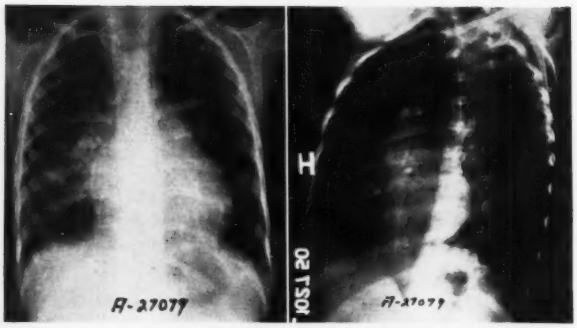


FIG. 3. Right ventricular enlargement superimposed on a mild left ventricular enlargement, as seen in a high ventricular septal defect (acyanotic stage). a. Posteroanterior projection. Note slight but definite increase in transverse diameter of the heart with increased convexity of the right border, not of atrial origin. b. Left anterior oblique projection showing definite increase in maximum transverse dimension with mild anterior bulge toward sternum. Here the enlargement of the right ventricular chamber is similar to that seen in combined mitral stenosis and insufficiency.

advocated,[2] have failed to increase accuracy in evaluating selective ventricular enlargements in the hands of the authors.

Hypertrophy Versus Enlargement. Cardiac chamber enlargement means disease. Disease may, of course, exist without enlargement. The heart does not necessarily respond to an abnormal load by enlargement in its external dimensions. The increased load may be met by hypertrophy of muscle fibers which in time may produce a thickened myocardium. This commonly takes place without increase in the external dimensions of the chamber. In fact, the internal dimensions of the chamber may be slightly diminished in the presence of increased "elastic resistance" of the wall and increased output of the heart. The fact that there may be no change in heart size in the presence of long-standing increased load met by cardiac hypertrophy has recently been reemphasized by Kleinfield and Redish.[3] In their study, 18 of 45 patients with sustained or progressive essential hypertension showed no change in heart size by teleoroentgenogram for periods of 5 to 20 years! That this is also a common experience in aortic stenosis and coarctation of the aorta has not been as readily recognized. In pulmonic stenosis of mild to moderate degree, absence of significant right ventricular enlargement appears to be common (fig. 1). In general, if a ventricle is working against increased resistance or pressure, it would appear that hypertrophy, with little change in size, is common. Increase in "flow work," that is, an increase in the volume of blood handled by the chamber per unit of time, such as is seen in extracardiac shunts or septal defects, appears to be more commonly associated with chamber enlargement (probably also with hypertrophy) early in life. These observations do not apply as well to the atriums which appear to be more distensible chambers.

CARDIAC BEAT

Observation of the amplitude of excursion of the cardiac border, main pulmonary artery, and aortic arch during fluoroscopy yields information on the state of the myocardium. A poor excursion of the cardiac border indicates either pericardial fluid or myocardial weakness, or both, and often preclinical failure may be recognized in this manner. Increased amplitude of pulsation of the pulmonary artery and aorta together indicates an extracardiac shunt, although a high septal defect with aortic insufficiency may give the same.

Interestingly enough, hypertrophy of the ventricle, as seen in hypertension, may be associated with a diminished amplitude of pulsation. However, this should cause no confusion, as in these instances there is relatively little chamber enlargement.

Actual thinning of the wall of a vessel may

be reflected by an increase in amplitude of pulsation even in the presence of low pressure and diminished flow. This is true in localized poststenotic dilatation of the pulmonary artery. Though the cause remains obscure, the dilated segment to which this increased amplitude of pulsation is limited is observed to be thinwalled at operation.

Pulmonary Vasculature

The authors are among those who have long emphasized the value of the pulmonary vasculature, as seen on roentgenograms, as an aid in the diagnosis of congenital heart disease. Excellent research on the relation of the pulmonary to the systemic circulations in congenital heart disease[4] and the correlation of this with roentgenoscopic observations[5] has added to and clarified what was previously clinical empiricism.

A film on full inspiration will give the best definition of the size and course of the pulmonary vascular tree. Fluoroscopy will supplement this information by revealing the presence or degree of pulsation of the vessels. Judging vasculature simply by the fluoroscopic screen "brightness" is a hazardous substitute for detailed examination of individual vessels on the film.

The normal vascular pattern observed on the roentgenogram is almost entirely the pulmonary arterial tree. The pulmonary veins, although adding density to the chest, normally are not recognized as a distinct pattern, probably because they are only approximately half the size of the pulmonary arteries for any given distance from the hilum. In addition, the pulmonary veins do not emerge from single trunks in the hilums, but emanate from the usually four pulmonary veins which lie behind the heart in the posteroanterior projection.

Pulmonary Vascular Engorgement. An increase in size, or more specifically, in caliber, of the normal arteries of the lung represents an increase in content of these vessels. This is vascular engorgement, pulmonary hyperemia, or the pleonaemic lungs of Campbell.[5] This change is not to be confused with those loosely termed as "prominent markings," a nondescript term commonly used to denote increased radial density of the lung without specification as to whether it be intravascular or extravascular in origin. The increased caliber of vascular engorgement of the arteries is best recognized in the middle third of their course as they traverse the lung field, and not in the hilum. The increased volume of blood in the pulmonary arterial tree may be the result of increased amount of blood flowing through these vessels, *an active vascular engorgement*; or it may be relatively static; *a passive vascular engorgement.*

Active or Passive Pulmonary Vascular Engorgement: The differentiation of active from passive engorgement cannot be made by examining individual vessels on the films. Supplementary information is necessary, which, however, often can be found on the films. Intrapulmonary congestion (extravascular fluid evidenced by an ill-defined increase in density of the bronchial or interstitial supporting tissues) suggests passive engorgement. Active expansile pulsation of the vessels at fluoroscopy is almost incontrovertible evidence that the engorgement is active and secondary to left-to-right shunt.

The recognition of active vascular engorgement is, of course, the *sine qua non* for radiologic evidence of left-to-right shunt. Without it, one may be at a loss as to whether the chamber enlargement is based on a stenotic lesion or an arteriopulmonary shunt. This is often the radiologist's dilemma in trying to recognize small shunts. In general, if chamber enlargement is unequivocally recognized, it may not be attributable to a left-to-right shunt unless active vascular engorgement is demonstrable, such is the parallelism in these lesions. Prominence of the main pulmonary artery is an exceedingly poor index of increased pulmonary blood flow, and it should not be attributed to this unless the increased flow is reflected by active pulmonary vascular engorgement in the lung.

Diminished Pulmonary Vasculature. Diminution in the caliber of the intrapulmonary vessels, as recognized on the roentgenogram, is indicative of diminished content in the vessels and is practically pathognomonic of diminished pulmonary blood flow. This is seen most

commonly in pulmonic stenosis of moderate or marked degree, with or without associated lesions of overriding aorta, atrial septal defect, and so forth. Diminished blood flow through the lung also occurs in tricuspid atresia or stenosis, Ebstein's disease, and anomalous insertion of a vena cava into the left atrium. By catheterization, we are recognizing an increasing number of cases of primary pulmonary hypertension of undetermined cause in which the obstructive phenomena appear to take place in the periphery of the pulmonary arterial tree (perhaps the congenitally high "elasticity resistance" of Deuchar and Knebel).[4] This group of patients also appears to have roentgenographic evidence of diminished pulmonary blood flow, at times making the x-ray differentiation between this condition and pulmonic stenosis exceedingly difficult.

Expansile Pulsation of Pulmonary Vessels. This is an actual increase in the dimensions or transverse diameter of the vascular shadow observed during systole at fluoroscopy. It is to be distinguished from the mere rhythmic movement of the vessel, secondary to respiratory activity, or transmission of pulsation by proximity to the heart or great vessels.

Normally, expansile pulsation may be seen in the main pulmonary artery and its primary divisions. Slight expansile pulsation of the secondary and, rarely, tertiary branches in the hilar shadow or lung root may be observed in hyperthyroidism, a hyperactive heart of excitement, or anemia. Technically, this is observed best while the patient is holding his breath, with the screen coned down to a square four to 5 cm. over the right hilum. This eliminates the transmitted pulsation due to the proximity of the main pulmonary artery so commonly seen in the left hilum. Individual vascular shadows should be fixed in the field of vision, preferably a vessel on end. If expansile pulsation is picked up in the right hilum, it should be followed out peripherally, and if it can be observed distal to the secondary and tertiary divisions of the hilum as one approaches the mid-lung fields, it can usually be considered abnormal. Almost invariably it means increased pulmonary blood flow.[5] The expansile pulsation is most commonly observed in atrial septal defects, high or large ventricular septal defects, and truncus communis. It is less commonly observed in patent ductus arteriosus, and is characteristically lost in the older age group if and when pulmonary hypertension intervenes. The mechanism involved in the production of increased amplitude of pulsation of the main pulmonary artery and expansile pulsation of the pulmonary vascular tree has recently been investigated.[5]

Evidence suggests that increased pulmonary flow is the dominant factor in production of the vascular prominence, and that it is also a factor in expansile pulsation. The stroke output of the right ventricle is probably more important in the latter. The increase in the pulmonary vascular expansile pulsation of the atrial septal defect and ventricular septal defect over the patent ductus arteriosus is explained by the fact that, in the former, cardiac output is forced into the arteries suddenly during systole, instead of more gradually during systole and diastole, as in patent ductus arteriosus. Pulmonary pressure probably plays a less significant role than flow in producing these pulmonary vascular changes.

"Hilar Dance" and "Hilar Sling". Campbell[5] pointed out that the "dance of the hilum" as originally described in 1925 was presented as being pathognomonic of pulmonary regurgitation, although review of the case notes today suggests that the patient had an atrial septal defect. Up to this point, we have avoided using this highly descriptive term because of the variable interpretations placed upon it throughout the literature.[5] Many use it synonymously with any hyperactive beat or pulsatile main or primary division of the pulmonary arteries. When used in this sense, it does not necessarily imply the presence of increased pulmonary blood flow or shunt. When used subsequently, it will mean an intrinsic vascular expansile pulsation observed lateral to the right hilar shadow.

Collateral Pulmonary Circulation. In many patients with deficient pulmonary blood flow, a collateral circulation develops through the bronchial arteries which is recognizable on roentgenograms of the chest. The diagnostic clue lies in the alteration of the vascular pat-

tern. The bronchial arteries pursue a considerably more tortuous course, lacking the linear radial distribution of the pulmonary arteries, and they fail to emanate from a central point in the hila (fig. 4 and 5). This appearance has recently been well described.[6]

It takes at least two to three years for this picture to develop, but it is common in patients having tetralogy of Fallot and in some having tricuspid atresia, particularly if they are doing well. It has never been observed in uncomplicated pulmonic stenosis.

Classification of Congenital Heart Anomalies

A practical clinical working classification of congenital heart anomalies cannot rest on a single yardstick or diagnostic instrument. A straight physiologic classification suffers the disadvantage of grouping diverse anatomic lesions under a single physiologic group. A completely anatomic classification lends itself only to adequate application at the postmortem table. A roentgenologic classification suffers the severe handicap of using predominantly anatomic criteria in a technic which falls far short in its revelations of gross anatomy. The radiologist is likely to overemphasize, in his necessarily simple classification, certain roentgenographically conspicuous anatomic features, particularly prominence of the pulmonary artery, just as the pathologist for years trivialized the physiologically important pulmonic stenoses and hypertension, simply because the structures appeared grossly normal, and he failed to appreciate the physiologic implications. Any classification, if it is to be helpful, must contain clinical, physiologic, and anatomic data. It is a relatively simple matter to classify the majority of cardiac abnormalities into similar physiologic groups. This can be done in approximately 85 per cent of the cardiac malformations in patients more than 2 years of age, using routine diagnostic methods. In the remaining patients it may be necessary to call upon the more complicated technics of angiocardiography and cardiovascular catheterization. A recent "correlation of the physiologic and clinical findings of the more common congenital malformations of the heart" has been published by Bing and his associates.[7] A major division of the cardiac malformations usually is made on a clinically recognizable physiologic feature: The presence, absence, or late appearance of cyanosis (table 1).

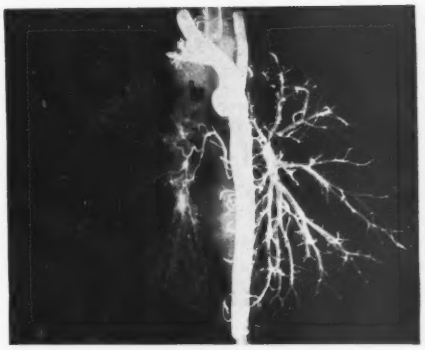


FIG. 4. Injection of the right pulmonary bronchial collateral channels and the left pulmonary arterial tree with radiopaque material for contrast to illustrate the difference in topography between the bronchial arterial tree (b) and the pulmonary arterial tree (p).

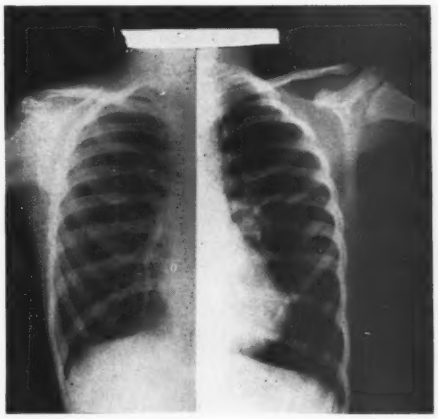
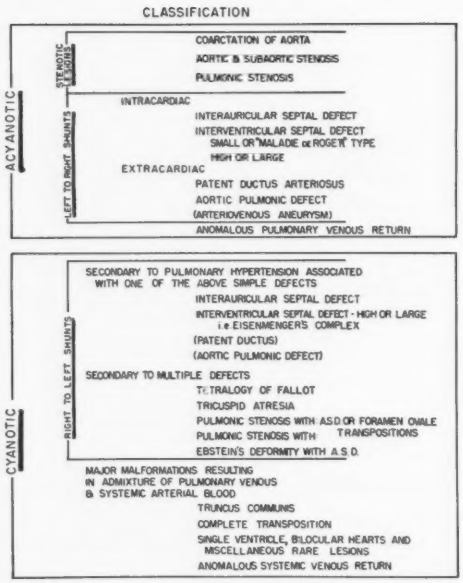


FIG. 5. "Split" film showing the pulmonary vascular pattern made up of predominantly bronchial collateral circulation secondary to tetralogy of Fallot: right lung. Pulmonary arterial vascular pattern of a normal left lung. In the right lung the uniformity of caliber, and tortuosity of the vessels are seen, with failure of emanation from a central point in the hilum. In the left lung field a radial emanation from the left main pulmonary artery with gradual tapering vessels and arborization may be seen.

Malformations of the acyanotic type are subdivided into those presenting evidence of

TABLE 1.

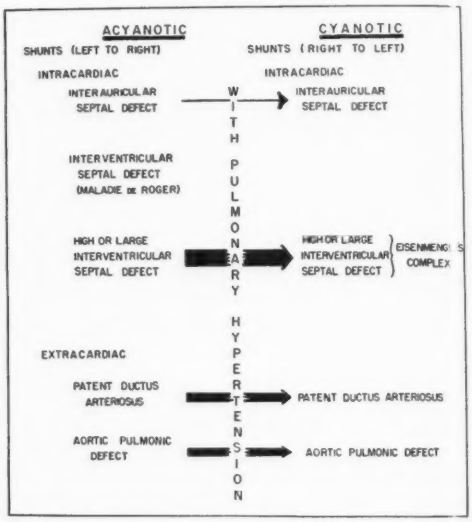


congenital stenosis as opposed to those presenting evidence of a defect between the pulmonary and systemic circulation permitting an abnormal shunting of blood from left to right.

If cardiac cyanosis is present, one may assume a flow defect between the pulmonary and systemic circulations in the opposite direction; namely, a right-to-left shunt.

If cyanosis is inconstant or has appeared later in life (usually fourth to sixth year) it is reasonable to assume, in the case of a congenital cardiac malformation, that a left-to-right shunt has reversed itself, with blood now flowing in the opposite direction, from right to left. This reversal is usually associated with pulmonary hypertension (table 2).

TABLE 2.—*Lesions Which Shift From the Acyanotic to the Cyanotic Group*



Left-to-right shunts, whether intracardiac or extracardiac may be theoretically reversed if the pressure in the pulmonary arterial system reaches or exceeds that of the systemic system. With this shift, the load on the heart is altered, the configuration reflects the altered load by x-ray, and cyanosis is usually recognized clinically. The table illustrates the lesions in which this mechanism of cyanosis has been observed; the thickness of the arrows indicates the frequency with which this shift from the one group to the other occurs. It becomes obvious that in this shift, the heart in each instance assumes a more balanced enlargement and loses its more distinctive selective features. Once the hearts have shifted to the right, they assume a uniform appearance and become essentially indistinguishable from one another. (See text under Eisenmenger's Complex.)

Acyanotic Group

Coarction of the Aorta. Usually, the diagnosis of coarctation of the aorta is readily established by clinical and roentgenologic examination. In the barium-filled esophagus, the site of the coarctation is often indicated by an indentation in the esophagus on the left, just below the level of the aortic arch. This indentation usually indicates a poststenotic dilatation of the aorta; multiple indentations or ring shadows of calcium in this area usually indicate intercostal aneurysms. Both of these significant complications of coarctation may now be dealt with surgically in the majority of cases by replacement of the coarcted segment by grafts.[8, 9, 10]

Abnormal pulsation of the left ventricle in the presence of coarctation usually suggests aortic insufficiency which is commonly the result of bicuspid valves.

Shallow bilateral notching of the lower margins of the ribs was formerly considered a pathognomonic sign of collateral circulation around an intrathoracic coarctation of the

aorta. Neurofibromatosis with multiple nodular lesions of the intercostal nerves, collateral circulation from bronchial vessels in tetralogy of Fallot, and, most recently, vascular notching produced by dilated tortuous intercostal veins resulting from collateral circulation of a longstanding obstruction of the superior vena cava, have been recognized as producing a similar appearance.[11] The actual visualization of the tortuous internal mammary arteries projecting from below the sternum into the lung fields on the plain lateral or oblique films is helpful evidence of collateral circulation.[12]

Coarctation as a cause of infantile cardiac failure has been increasingly recognized at this Clinic. Death during infancy, as a result of cardiac failure secondary to coarctation, is not an unfamiliar picture to the pathologist. Unfortunately, the clinician and radiologist have not been so aware of this occurrence. They usually see the child after myocardial failure has set in, and the clinical picture is one of cardiac decompensation and myocardial strain. Perhaps too often the findings are attributed to primary myocardial disease, as careful comparative blood pressure studies between the upper and lower extremities are not commonly done in this age group. Radiologic examination is of little help in this problem except that the examiner should constantly be suspicious of a possible coarctation when seeing an infant in cardiac failure without evidence of a large left-to-right shunt, cyanosis, or major malformation at the base of the heart.

The stark pessimism felt by clinicians in the past regarding the infant in cardiac failure secondary to coarctation of the aorta is probably not justified in light of recent experiences[13] in which 10 or 12 of these infants in failure have been carried through the period of adjustment to the coarctation during the rapid infantile growth by strictly medical measures. Thus, they have been carried on to the age at which surgical correction may be carried out.

Aortic and Subaortic Stenosis. Congenital aortic and subaortic stenosis is not a roentgenologic diagnosis, and is more often missed than recognized by x-ray examination. Characteristic is isolated left ventricular hypertrophy identical to that seen in hypertension, aortic insufficiency, or coarctation of the aorta. In congenital aortic stenosis this is often recognized only late in life when hypertrophy is accompanied by considerable enlargement. Campbell recently emphasized that the delayed appearance of symptoms and signs accounts for many cases not being recognized until middle life. The congenital nature of the lesion is thus perhaps not suspected as often as it should be. Acquired myocardial fibrosis and valvular calcification add to the difficulty in the differential diagnosis of this lesion from acquired aortic valvular disease of rheumatic origin in older individuals. A roentgenologic clue to the diagnosis of these conditions may be found in the great vessels. The aorta is commonly dilated; apparently this is poststenotic dilatation with widening of the arch and increased caliber of the ascending aorta. In a rarer form, the aorta presents diffuse hypoplasia in that it is unusually small in caliber throughout.

Pulmonic Stenosis. This condition is characterized by congenital narrowing of the tract through which the blood flows from the right ventricle to the lungs. The resulting degree of obstruction is variable. It may be exceedingly mild or severe. The roentgenologic and clinical appearance parallels this same scale of severity, yet the correlation is not 100 per cent. The stenosis may be of such mild degree as to produce no recognizable structural changes. If changes exist, the one constant finding is right ventricular enlargement. If the intrapulmonary blood flow is considerably reduced as a result of the stenosis, the pulmonary markings throughout the lungs will be diminished in caliber on the x-ray films. In most moderate and severe pulmonic stenoses the right atrium is also slightly enlarged. In patients with pulmonic stenosis of sufficient severity to give rise to symptoms, the pulmonary vasculature is always diminished, and in about half of those without symptoms the vasculature can also be recognized as diminished.

Recently, much emphasis has been placed on the actual location of the narrowing in the right ventricular outflow tract. The narrowing

may be in the infundibulum (as a generalized narrowed tract or small annulus), in the valve ring, in the pulmonary valve leaflets, in the pulmonary artery itself, or in a combination of these.

Valvular Stenosis With Poststenotic Dilatation: In uncomplicated ("pure") pulmonic valvular stenosis there is usually an associated poststenotic dilatation of the main pulmonary artery which may extend into the left and right branches for a short distance, but is poorly visualized on the right because of its deep retroaortic and prespinal location. This poststenotic dilatation is recognizable roentgenologically as a prominent convexity of the middle cardiac segment, along the left border of the cardiac silhouette below the aortic knob and above the left ventricle.

Fluoroscopically, one may observe a frank expansile or exaggerated systolic pulsation of this prominent pulmonary artery segment; however, the expansile pulsation is limited only to the main pulmonary artery segment. There is never an expansile pulmonary pulsation involving the secondary, tertiary, or smaller vessels. This prominent pulsation of the pulmonary artery probably represents the "pulmonary artery aneurysms" of the early radiologic literature. Recently, two patients with gross "idiopathic dilatation" of the pulmonary artery have been described who had normal pulmonary arterial and right ventricular pressures, but had pulmonic incompetence.[14]

Valvular Stenosis Without Poststenotic Dilatation: That uncomplicated valvular stenosis can exist without poststenotic dilatation is now well established.[14, 15] Patients with this condition present a normal-appearing pulmonary artery segment.

Infundibular Stenosis Without Poststenotic Dilatation: Uncomplicated ("pure") infundibular stenosis with normal valves is rare. Isolated examples have been reported.[14, 16, 17, 18] In most of these, the pulmonary artery may be recognized, but it is usually small. In the narrowed or annular type of infundibular stenosis, a poststenotic dilatation of the distal infundibulum may at times be seen, representing almost a separate infundibular chamber. This is one of the rare examples where one recognizes enlargement of the pulmonary conus. It presents itself roentgenoscopically as a prominence or bulge of the cardiac contour just below the origin of the pulmonary artery and is best seen in a mild right anterior oblique projection. It lies considerably anterior to the prominence, often seen at the same level, produced by the left atrium.

Angiocardiography in Pulmonic Stenosis: Angiocardiography adds little of value in differentiating infundibular and valvular pulmonic stenosis, except when carried out as in Sweden by direct intracardiac injection and rapid serialographic roentgenography (10 to 12 films per second).[19, 20, 21]

Septal Defects. Interauricular Septal Defect: Exceedingly small defects, although they may give rise to significant murmurs, may produce no change in the appearance of the heart. If the shunt is of sufficient magnitude to produce roentgenographic changes, right ventricular enlargement will always be recognized. Larger shunts will sooner or later be reflected by increased prominence of the pulmonary vascular markings, and there may be prominence of the atria, especially the right. There is usually an increased amplitude of excursion of both the right and left ventricular walls and commonly an expansile pulsation of the intrapulmonary vessels. If roentgenographic changes are present, the electrocardiogram should show incomplete right bundle branch block.

Actual demonstration of the atrial defect by angiocardiography, using an extremely rapid injection technic and simultaneously recording an electrocardiogram with roentgenologic exposures of 10 to 12 films per second, has recently been reported.[19] These studies suggest that the foramen ovale normally closes between birth and the sixth day of life, that its delayed closure may play a role in "asphyxia neonatorum," and that the congenital auricular defect varies in size during the cardiac cycle, being smallest at the height of auricular systole.

Lutembacher's syndrome, the coexistence of an atrial septal defect and mitral stenosis, in the few confirmed cases, does not differ roentgenographically from a large atrial septal defect, as the effects of each lesion are similar

and additive. Actually, it has been shown recently that this combination of lesions is exceedingly rare, and the association of a "mitral-like" diastolic murmur with congenital lesions is common in the absence of mitral disease.[22] In our experience, many of the cases diagnosed clinically as Lutembacher's syndrome turn out, on further investigation, to be Eisenmenger's complex.

Interventricular Septal Defect (Maladie de Roger): This section includes only the small or low interventricular defects traditionally known as maladie de Roger. Physiologically, they behave quite differently from the larger or high defects to be discussed later. These defects are commonly responsible for a loud murmur with no recognizable roentgenologic changes. Although this defect throws an abnormal load on both ventricles, the roentgenologic evidence of the lesion is first recognized as right ventricular enlargement. Both ventricles usually hypertrophy. However, the right ventricle is probably more distensible, and enlarges first. The left ventricle hypertrophies to a considerable degree before there is roentgenologic evidence of enlargement. As the hypertrophy of both ventricles may be such as not to disturb the relationship of the left to the right, the dominance of the left over the right may be similar to the normal on the electrocardiogram. Thus, in patients with this lesion, it is not uncommon to see prominence of the right ventricle on the roentgenogram and dominance of the left ventricle on the electrocardiogram. The lungs may reflect the increased blood flow by engorgement of the vessels, and "hilar dance" may be present, but is not common. If pulmonary vascular engorgement is present, the left atrium will reflect this increased blood flow by slight prominence.

Persistent Patent Ductus Arteriosus. Here again, as in the interventricular septal defects, the small shunts usually behave physiologically differently from the large shunts. The classic radiologic picture with five roentgenologic criteria has been well described[23] as: left ventricular enlargement, prominence of the main pulmonary artery, left atrial prominence, pulmonary vascular engorgement (often with expansile pulsations) and a "hyperactive beat" along the entire left border of the heart with the pulmonary artery and aorta sharing in the hyperactivity. Any one or a combination of these changes may be present, but the experienced examiner will recognize in this pattern a parallelism of the size of the left ventricle, the degree of pulmonary vascular engorgement, and the prominence of the left atrium.

The characteristic machinery murmur with an essentially normal heart and the hemodynamic pattern just described was formerly accepted as the *sine qua non* of the diagnosis of persistent patency of the ductus arteriosus. An increasing number of patients in recent years have been found to have a patent ductus either without a machinery murmur, or presenting no murmur or one limited to systole. The risk of error in diagnosis in these cases has recently been emphasized.[24-29] In our experience, patients lacking the classic murmur or the previously described x-ray appearance fall into two distinct categories: (1) patent ductus arteriosus with myocardial failure, and (2) patent ductus arteriosus with pulmonary hypertension. The patent ductus arteriosus in failure looks like any other heart in failure. There is generalized enlargement and pulmonary engorgement of a passive type, often associated with congestion. It is obvious that, as a result, it loses its radiologic distinctive features. In the exceedingly large patent ductus, with or without pulmonary hypertension, failure is not a rarity in infants, and we can add the patent ductus to the previously discussed coarctation and primary myocardial disease, as a diagnosis which must be entertained when an infant with acyanotic heart disease is presented in failure with a large heart, pulmonary engorgement, and congestion.

Patent Ductus Arteriosus With Pulmonary Hypertension: If pulmonary hypertension is associated with patent ductus arteriosus, the additional load on the right side of the heart will be reflected by right ventricular hypertrophy and often enlargement. If this is superimposed on the previously described characteristic changes of a patent ductus, the resulting cardiac configuration is one of a

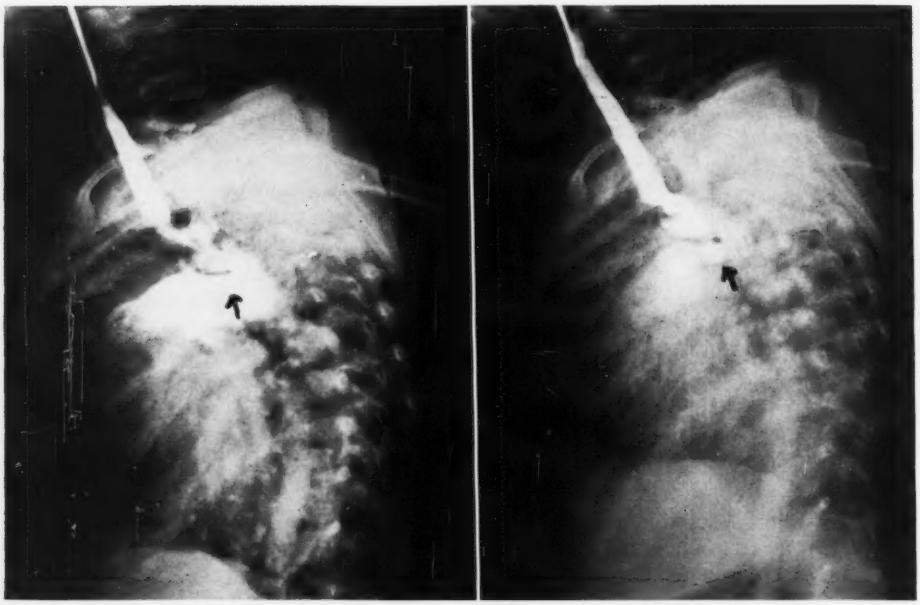


FIG. 6. Retrograde aortogram in the left anterior oblique position, demonstrating the contrast material injected in the left carotid artery passing down the aorta and simultaneously through a large ductus (arrow) into the pulmonary artery. The retrograde aortogram has specific application in the identification of the atypical patent ductus (as illustrated in this patient with no cardiac murmur) and in the differential diagnosis of the high, large ventricular septal defect, patent ductus arteriosus, and the aortic pulmonic defect (fig. 7).

balanced load with both right and left ventricular enlargement, a prominent pulmonary artery, pulmonary vascular engorgement, left atrial prominence, and often a hilar dance.

These variations in appearance of the ductus are often referred to as the "atypical patent ductus." Actually, we believe that the situation would be much clarified if these were thought of strictly in terms of complications of the ductus. Instead of referring to them as "atypical," they could be thought of as patent ductus complicated by cardiac failure or patent ductus complicated by or associated with pulmonary hypertension. These complications are expressed by an additional character in the configuration of the heart.

Thus, it becomes obvious that the patent ductus with either of these complications loses its distinctive features and is no longer readily recognizable by everyday diagnostic technics. It is here that retrograde aortography becomes a definitive procedure.[30, 31] In fact, this procedure is definitely indicated for any acyanotic patient with nondescriptive murmurs in whom a patent ductus cannot be excluded with certainty, clinically, and who shows active pulmonary vascular engorgement for the more or less balanced right and left ventricular enlargement and a wide systemic pulse pressure. Only by this means can this important surgically correctible lesion be finally diagnosed (fig. 6). In the presence of patent ductus arteriosus, the aortogram shows prompt opacification of the pulmonary artery, the injected dye passing directly from the aorta to the pulmonary artery, as a result of a left-to-right shunt through the ductus (fig. 6).

Aortic Pulmonic Defect or Aortic Pulmonic Fenestration. This congenital malformation is characterized by fenestration between the ascending aorta and the main pulmonary artery, anatomically similar and only slightly removed from the location of the patent ductus arteriosus. In consequence, it places an identical hemodynamic load on the heart, resulting in a roentgenographic and roentgenoscopic

ppearance which may be identical with that f the patent ductus arteriosus. If the ductus-ke murmur is slightly lower and to the right f its usual position, this diagnosis must be ntertained.[30, 32, 33]

High or Large Interventricular Septal Defect. This intracardiac congenital defect resulting n a left-to-right shunt was not taken up with he "maladie de Roger" with which it is natomically akin, but is discussed together with the patent ductus and the aortic pulmonic defect because it gives an identical hemodynamic disturbance and places the same type of load on the heart as the patent ductus and the aortic pulmonic defect.

The explanation is somewhat complex, but it may be simplified by pointing out that the intracardiac dynamics are such that the blood is shunted directly through the defect during systole from the outflow track of the left ventricle into the conus of the infundibulum of the right ventricle, and on to the main pulmonary artery. Thus, its physiology is similar to that of aortic fenestration in which the blood is directed in a left-to-right shunt from the base of the ascending aorta into the base of the pulmonary artery, or even to the patent ductus where the blood is shunted from the descending aorta directly into the pulmonary artery.[34] The left half of figure 7 illustrates schematically the slight anatomic differences of these three lesions and their physiologic similarity. Here again is a definite indication for the retrograde aortogram. The differential diagnosis in these anatomically slightly dissimilar and physiologically similar lesions can often be made only by retrograde aortic injection (fig. 6).

The Shift from Acyanotic to Cyanotic Group

Pulmonary Hypertension. Pulmonary arterial hypertension as the result of increased pulmonary resistance may occur alone without cardiac lesions, or be associated with, or secondary to, congenital heart disease.[35]

Primary pulmonary hypertension is not necessarily associated with a cardiac murmur, but it is reflected in the heart by right ventricular enlargement, prominence of the main pulmonary artery, and, eventually, diminution in the caliber of the peripheral pulmonary vessels. The appearance is similar to that of cor pulmonale in the adult.

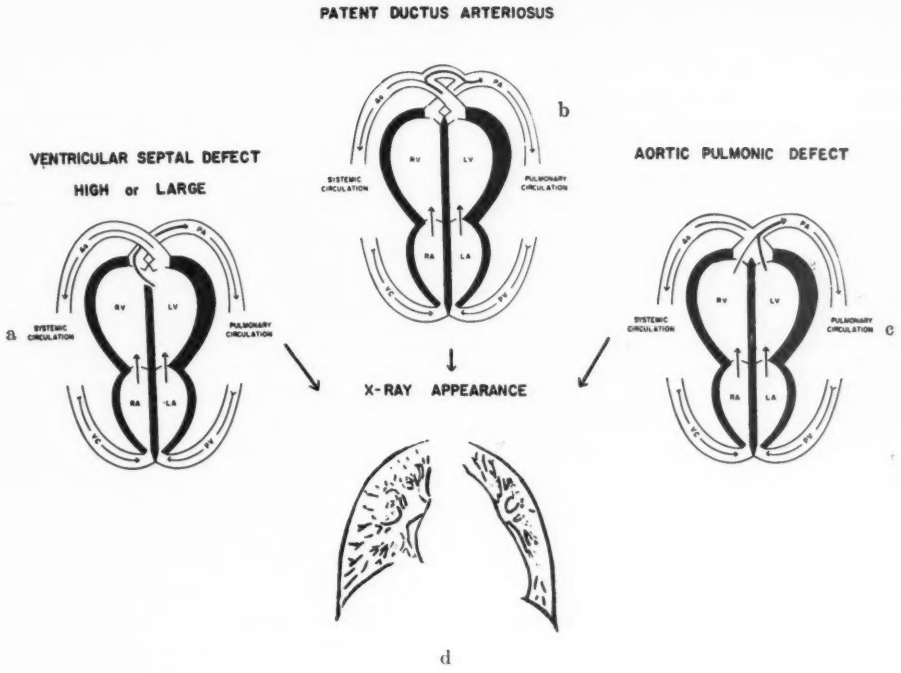
The clinical aspects and the role of pulmonary hypertension in congenital heart disease have been well evaluated recently by Nadas.[35] Without entering the controversy of the mechanism involved in the pulmonary bed, resulting in increased pulmonary resistance and pulmonary hypertension, it can be said that there is evidence that prolonged pulmonary hypertension causes secondary changes in the vascular bed, which in turn may cause a progressive rise in pulmonary arterial pressure as well as an irreversible resistance.[29, 36, 37] On the other hand, it is believed that under certain conditions the pulmonary vascular bed may retain its fetal characteristics.[38, 39] Be that as it may, it can be said empirically that equalization of pressures between the systemic and pulmonic circulation is found in certain types of malformations and apparently under certain circumstances. In our experience, pulmonary hypertension of sufficient degree to cause a significant change in the cardiac silhouette is found in two general circumstances: in large interventricular septal defects or in large extracardiac shunts (patent ductus arteriosus, aortic-pulmonic defect). In the latter equalization of pressures between the pulmonary and systemic circulations takes place promptly in infancy. It could be speculated that this is possibly a reflex action of the complex neurocirculatory system which is made to sustain the systemic pressure and which is necessary to sustain life. It should be obvious that if the size of the defect shunting blood in the septum or aorta into the pulmonary artery approaches the caliber of the aorta itself in size, pulmonary pressure must rise to, or approach, systemic pressure in order to get enough blood through the systemic circulation to sustain life. If this did not take place, the child would, in effect, bleed to death through the hole in the side of the aorta into the pulmonary capillary bed (figs. 6 and 7).

Clinical empiricism also dictates that in certain congenital malformations of the heart, equalization of the pressures between the

systemic and pulmonic circulation takes place, or progresses slowly, considerably after infancy. These have been customarily thought of as an acquired secondary type of progressive pulmonary hypertension. It is in this group that the pathologic mechanism is still controversial. Be that as it may, clinical observation of the patients and the heart, recently documented by catheterization studies, indicate a gradual progressive increase in pulmonary pressures with resulting reversal of the shunt and onset of cyanosis. This picture occurs classically in the high or large ventricular septal defects, but the same mechanism and the same sequence of events may take place in other intracardiac and extracardiac left-to-right shunts (table 2). Thus, we make the transition from the acyanotic to the cyanotic group.

Interventricular Septal Defect With Pulmonary Hypertension (Eisenmenger's Complex). Anatomically, this malformation is characterized by high interventricular septal defect or large interventricular septal defect with a functionally overriding aorta and a potential left-to-right or right-to-left shunt, depending on the pulmonary vascular resistance. As a result, if the defect is huge, vascular pulmonary hypertension must take place promptly in order to sustain life, and the result is the infantile picture just described. If the defect is relatively small, there may be a left-to-right shunt in early life with increased blood flow through the pulmonary circulation. The resulting picture is identical to that previously described for patent ductus arteriosus. Later in life, if pulmonary hypertension supervenes or progresses, as often occurs between the ages of 6 to 12 years, there may be a reversal of the shunt from right to left, with the gradual onset of cyanosis. However, the group of cardiac malformations in which cyanosis appears relatively late in childhood is not mad up entirely of the high ventricular septal de fects (table 2). This equalization of the loa on the right and left sides of the heart in th interventricular septal defect, patent ductu arteriosus, and aortic-pulmonic defect result in a picture which is roentgenographically and at times clinically, identical, so that it i difficult to determine what the original lesio was. In fact, let us recognize that the physio logic changes in this group are the same; th anatomic site of the shunt is only slightl different. The development of this appearance as a result of pulmonary hypertension in an intracardiac or extracardiac left-to-right shunt with resulting reversal of the shunt and de velopment of cyanosis, has loosely been calle the "Eisenmenger physiology." This, of course is based on a marked similarity in appearanc and behavior. Because of the nonspecificity of the appearance, we would much prefer to indicate the change by that factor which is most important in bringing it about; namely, pulmonary hypertension. One might designate the condition, if the anatomic diagnosis is not known, as "cardiac enlargement secondary to left-to-right shunt, with pulmonary hypertension." The term "Eisenmenger's complex" could be dropped entirely, and in the acyanotic stage the lesion could be specified as "high ventricular septal defect with left-to-right shunt." When the peripheral blood in these cases becomes somewhat unsaturated, it might be specified as "high ventricular septal defect with pulmonary hypertension and right-to-left shunt." Such reversal of flow, long familiar in the high septal defects, has become recognized with increasing frequency in other lesions, especially in the patent ductus.[40, 41, 42] That recognition of this physiologic change is exceedingly important is testified to by the fact that once pulmonary hypertension has

FIG. 7. Diagram illustrating the slight anatomical differences resulting in a very similar physiology of the high ventricular septal defect, the patent ductus arteriosus, and aortic pulmonic defect (a, b & c). Due to the similarity of the load on the heart, the x-ray appearance may be identical for the three lesions (d). With the complication of increased pulmonary resistance and resulting pulmonary hypertension, the physiology is grossly altered, the shunt reversing to a right-to-left, (a_1, b_1 & c_1) and this altered load is reflected by the balanced right and left ventricular enlargement, large pulmonary arteries and hilar shadows persist but the mid and peripheral lung fields show relative diminution in caliber (so-called Eisenmenger configuration d_1).


PATENT DUCTUS ARTERIOSUS
VENTRICULAR SEPTAL DEFECT
HIGH or LARGE
a
b
AORTIC PULMONIC DEFECT
c
SYSTEMIC CIRCULATION
PULMONARY CIRCULATION
RV
LV
RA
LA
X-RAY APPEARANCE
d

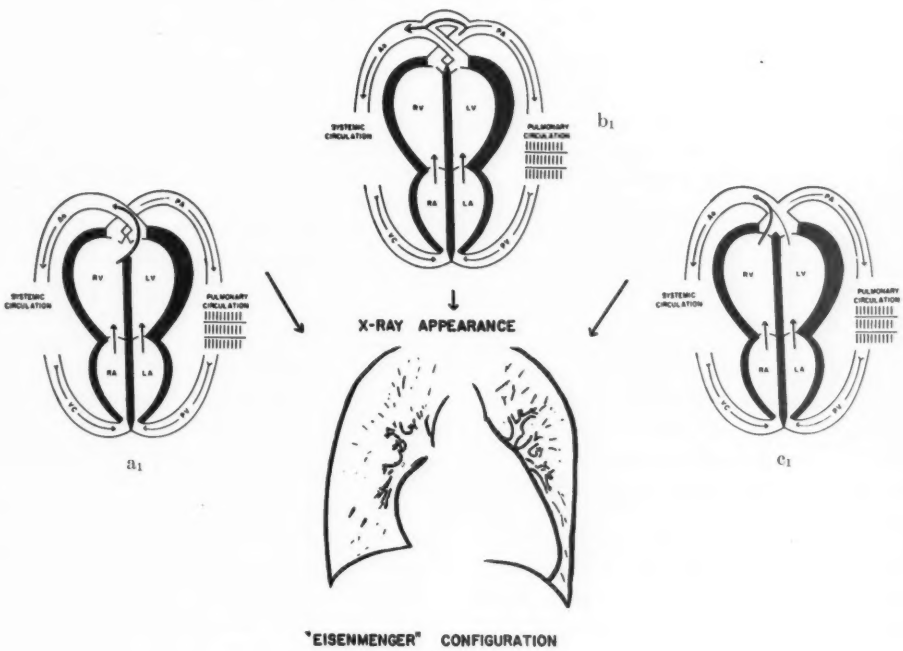

INCREASED PULMONARY RESISTANCE + PULMONARY HYPERTENSION
a1
b1
c1
SYSTEMIC CIRCULATION
PULMONARY CIRCULATION
X-RAY APPEARANCE
"EISENMENGER" CONFIGURATION
d1

FIG. 7

set in, and particularly if it has been long standing, it may become irreversible. In this case, surgical closure of the patent ductus is an extremely hazardous procedure, and, in fact, of questionable therapeutic benefit.

Cyanotic Group

If we considered all the possible malformations causing cyanosis in the neonatal period in this discussion, we would be preoccupied with innumerable and sometimes monstrous curiosities of the obstetrical nursery and postmortem room. In considering only those malformations which permit survival for 18 to 24 months or more, we find that the majority, perhaps 60 to 70 per cent, are made up of the tetralogy of Fallot. Thirty to 40 per cent are predominantly made up of the tricuspid atresias, truncuses, and well-compensated transpositions. A minority of this latter group are composed of the rarer and exceedingly complex multiple lesions which challenge us constantly in differential diagnosis and call upon the maximum in diagnostic aids, including catheterization, angiocardiography, and so forth.

The most rewarding single roentgenographic sign in subdividing the cyanotic group is abnormal pulmonary blood flow, as recognized by an increase or diminution in the caliber of the pulmonary vascular markings. Tetralogy of Fallot and pure tricuspid atresias usually present diminished pulmonary vascular markings as a result of the decreased pulmonary blood flow. Truncus communis invariably presents pulmonary vascular engorgement, evidenced by prominence of the vessels, often associated with an expansile pulsation or "hilar dance." The appearance of the transpositions is entirely dependent on the compensating associated lesion permitting the transfer of blood from the left to the right. However, the majority of the transpositions, unless some degree of pulmonary stenosis exists, present evidence of pulmonary vascular engorgement.

Tetralogy of Fallot. The roentgenologic appearance is determined by the degree of pulmonary stenosis and the functional degree of overriding of the interventricular septum by the aorta. Variations in the degree of the pulmonic stenosis or overriding of the aorta result in a wide range of appearances from that approaching a normal heart (in which the pulmonic stenosis is mild and the overriding minimal) to that of the extreme "coeur en sabot" (in which the pulmonary artery is atretic and the aortic overriding marked, that is, pseudotruncus). There are all intermediates.

As the ventricular enlargement is purely right and the left ventricle is either normal or may be even somewhat hypoplastic, the enlargement is not reflected in the postero-anterior projection by an increase in the transverse diameter of the cardiac silhouette. In fact, in moderate to severe cases, the heart may appear smaller than normal. The heavy right ventricle dips into the diaphragm and elevates the apex of the heart, accounting for the "sabot" appearance. The cardiac waist is usually narrowed because of the absence or hypoplasia of the main pulmonary artery, and the beat in this middle cardiac segment on the left is either absent or diminished. In the left anterior oblique projection the heart appears almost round. Approximately one-fourth of the patients with this condition show evidence of a right aortic arch. The pulmonary vasculature, except in the exceedingly mild cases, is almost uniformly diminished.

If the patient survives a number of years, considerable collateral circulation through the bronchial arteries usually develops, and at first glance, this may mask the apparent diminution in the pulmonary blood flow. On closer examination, the distinctive pattern can be seen (fig. 4). These collaterals can make surgical dissection of the lung root exceedingly hazardous.[10]

It is widely agreed[43] that in at least 90 per cent of cases of tetralogy of Fallot the obstruction is infundibular in position. Brock,[18] on the other hand, feels that valvular stenosis in the tetralogy is considerably more frequent "if sought for carefully and properly." From the radiologic point of view it should be emphasized that in tetralogy of Fallot, it is exceedingly uncommon to see gross post-stenotic dilatation of the pulmonary artery.

Tetralogy of Fallot With Unilateral Atresia

of the Pulmonary Artery: A rare variant of the tetralogy, which in addition to the usual features presents atresia of one of the main branches of the pulmonary arteries, has been reported.[44] Roentgenographically, this may be recognized by a discrepancy in the vasculature of the two lungs. Instead of a uniform diminution of the pulmonary vascular pattern in both lung fields, the side with the atretic pulmonary artery will show considerable diminution of the pulmonary vasculature, whereas the opposite lung field will show a dilated main pulmonary artery, compensatory pulmonary vascular engorgement, and occasionally even a "hilar dance." Angiocardiography may confirm the absence of the pulmonary artery distal to the atresia on the affected side. This deformity considerably increases the risk of an operative shunt procedure. Atresia of one of the branches of the pulmonary artery in the absence of a tetralogy or any other abnormality has been recognized for some time.

Tricuspid Atresia. This is one of the few entities which may present a distinctive, almost pathognomonic, cardiac silhouette; namely, absence of mass where one is accustomed to seeing the right ventricle.[34] Unfortunately, less than 20 per cent of the tricuspid atresias present this appearance.[45] The majority have a "coeur en sabot" configuration indistinguishable from tetralogy of Fallot, but they have a definite distinctive feature in that the electrocardiogram almost uniformly presents evidence of left ventricular hypertrophy instead of the characteristic right ventricular hypertrophy of the tetralogy of Fallot. In our experience it is the enlarged right auricle (probably a function of the size of the auricular septal defect) which fills in the space normally occupied by the right ventricle and accounts for the "coeur en sabot" silhouette. Thirty per cent of the patients with tricuspid atresia are found to have extroposition or dextrocardia, and approximately 30 per cent, irrespective of the position of the heart, have reversal of the position of the aortic arch.

A new, and probably helpful radioscopic sign of tricuspid atresia has been reported.[46] This is an asynchronous pulsation of the anterior and posterior borders of the heart in the left oblique position. It is attributed to the replacement of the right ventricle, normally the main component of the anterior border, by the enlarged right atrium.

Pulmonic Stenosis With Atrial Septal Defect or Foramen Ovale. In this combination of lesions there are sufficient deviations from the classic signs of uncomplicated pulmonic stenosis to make it probable that in a given case a pattern will emerge which is incompatible with either pulmonic stenosis or auricular septal defect alone. If the patient is cyanotic, one must assume that the pulmonic stenosis is severe and dominant, thus reversing the septal shunt to a right-to-left flow. In the roentgenologic appearance of the heart, the pulmonic stenosis dominates, with prominence of the auricles. If cyanosis is present there will be right ventricular enlargement, auricular prominence, and pulmonary ischemia, as evidenced by diminution of the pulmonary vasculature. This conforms with our experience and recent reports of others.[14, 15, 47]

It is important to recognize that this combination of lesions may give rise to cyanosis at birth, but in the majority of patients, the onset is later. In the vast majority there is poststenotic dilatation of the main pulmonary artery. This combination of lesions becomes exceedingly important in the differential diagnosis with tetralogy, as they do not respond well to shunt procedures, and valvulotomy appears a more rewarding procedure.

Ebstein's Disease. This deformity, represented by a congenital downward displacement of the tricuspid valve into the right ventricle, has aroused considerable interest since Ebstein's original description in 1866, as it represents a distinct pathologic entity. In the presence of an auricular septal defect, which is the most commonly associated lesion, cyanosis always results.

In our experience the roentgenologic appearance of the heart is characterized by distinctive features which, however, are not necessarily specific for this entity. It presents a pure, exaggerated, right-sided enlargement with diminished prominence of the pulmonary vascular markings. Thus, the heart may be described

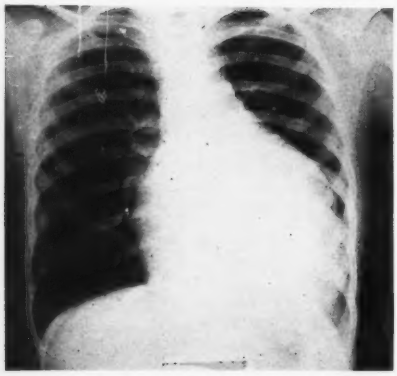


FIG. 8. Cardiac configuration in Ebstein's deformity. Note unusual prominence of right side with frank diminution of the main segment of the pulmonary artery and pulmonary vasculature, suggesting that insufficient blood is passing out of the right side of the heart.

as having the shape seen in severe auricular septal defect with the auricles, particularly the right, unduly prominent. However, there is not the expected prominence of the pulmonary artery or pulmonary vasculature (fig. 8). In fact, the pulmonary artery and vasculature are diminished. This is, of course, the result of some of the blood bypassing the lungs through the right-to-left shunt across the auricular septal defect. Whenever these changes are present and cyanosis is severe, Ebstein's disease should be suspected, particularly in the presence of arrhythmias or electrocardiographic abnormalities. A number of these cases have now been diagnosed clinically.[48]

Truncus Arteriosus Communis. This lesion usually can be recognized by a balanced right and left ventricular enlargement and a broad prominent vascular arch with lung fields which usually show evidence of active pulmonary vascular engorgement, often with associated "hilar dance." At fluoroscopy, the main pulmonary artery is observed to be absent by lack of the normal prominence and beat. This last characteristic is much more helpful in the differential diagnosis in the younger age group than evaluating the width of the upper part of the mediastinum. The prominence of the lung markings readily distinguishes this group of malformations from the tetralogies.

Transpositions of the Great Vessels. There are almost innumerable variations from the complete transposition in which the aorta arises from the right ventricle and the pulmonary artery from the left ventricle to variable degrees of overriding of the two ventricles by one or both of these vessels. Many of these malformations now travel in medical parlance under proper names which help to obscure their anatomic identity rather than emphasize their kinship based on the common denominator that in all these cases the basic malformation is the abnormal origin of the major vessels.[49, 50] The so-called "Taussig-Bing malformation" represents such a variation. Here the aorta arises from the right ventricle, while the pulmonary artery arises mainly from the right ventricle, but partially overrides the ventricular septum, receiving blood from both ventricles. Thus, there is cyanosis from birth. Roentgenograms show combined ventricular prominence with a large pulmonary artery, pulmonary vascular engorgement and "hilar dance."

Generalizations on the clinical aspects, the course of the disease, the murmurs, the electrocardiographic findings, and particularly the roentgenographic appearance of the heart are not valid in transpositions. This is due to the fact that these will all be dependent on the associated defects which compensate for the transposition by permitting admixture of blood from the right and left sides of the heart. One common observation will be the abnormal relationship of the base of the aorta and pulmonary artery to the heart, usually characterized by a mediastinal shadow narrowed in the frontal projection and widened in the left anterior oblique view. To evaluate the remaining characteristics, one must think in terms of transposition compensated by atrial septal defect and patent ductus, or transposition with ventricular septal defect. Equally important is the size of these defects. Thus, there is much variation in this group.[51, 52, 53]

Eighty-six per cent of the patients with transpositions die by the end of the first year, although patients have been reported to have lived to the age of 56 years without significant physical limitations. In the presence of an ab-

normal electrocardiogram, progressive cyanosis, and rapid increase in size of the heart, the diagnosis usually can be suspected in the first few weeks or months of life.

Anomalous Systemic Venous Return. Anomalous insertion of the superior or inferior vena cava or both into the left atrium is extremely rare, and clinically it is almost impossible to diagnose. Per se, this condition need not give rise to murmurs, but in most cases there is an associated congenital cardiac defect. Cyanosis is present, though not necessarily severe. Anatomic studies indicate that anomalous insertion of a persistent left superior vena cava is more likely than a right. Angiocardiography is probably the only method of making a definitive diagnosis.

As the curative potential of surgery should be so great in this type of deformity, one is constantly intrigued by the possibility of diagnosing this lesion, and it is probably a sound clinical policy to make all angiocardiograms for cyanotic children by means of a left-sided injection because of the greater chance of visualizing an abnormal insertion of a persistent left vena cava.

Anomalous Pulmonary Venous Return. As a result of a congenitally abnormal insertion, blood returning from the lungs via the pulmonary veins may drain into the superior vena cava, innominate, azygos, or subclavian veins, or into the right atrium. If there is complete drainage of pulmonary blood into the right side, an atrial septal defect usually exists to sustain life. More common is partial drainage of the pulmonary blood into one of these structures by way of abnormal insertion of one or more of the pulmonary veins. If more than 10 per cent of the pulmonary venous blood drains into the right atrium, important clinical signs may be expected. Conventional chest roentgenograms may present a characteristic appearance, as has been reported by Snellen and Albers.[54] The abnormal vessels are then recognized low and lateral to the right border of the heart, with the upper part of the mediastinum widened, resulting in a "figure of 8" mediastinal silhouette[54] (figs. 9 and 10).

Primary Myocardial Disease. In evaluating cardiac disease in children, particularly in infants, a number of patients will be found who have neither rheumatic nor congenital heart disease. This group recently has been well studied by Rosenbaum and his associates,[55] and clinically, these patients are found to have certain features in common: cardiomegaly, absence of significant murmurs, electrocardiographic abnormalities, and normal blood pressure. Their patients all had primary myocardial disease.

By the time these patients are examined, they present almost uniformly similar roentgenologic appearances. The heart is generally enlarged, all chambers sharing. There is a diminished excursion of the beat. The main vessels are normally placed, and the pulmonary vasculature is either normal or shows passive engorgement with congestion. The picture is that of a failing myocardium. Although at least five underlying pathologic entities have been shown to be involved (glycogen storage disease, aberrant left coronary artery, medial necrosis of the coronary arteries, subendocardial sclerosis, and idiopathic myocarditis), once the myocardium fails, the radiologic picture becomes the same. It is of interest that the first three of these entities fail to respond to any form of therapy, while the latter two may respond.[55]

Angiocardiography

The value of angiocardiography in the research laboratory and as a teaching medium has been established. As a diagnostic clinical instrument it has a limited but specific place.

Clarification of the limitations of cardiac angiography have only recently been stressed in the literature.[56] Important among these are: a. A certain concentration of radiopaque substance is necessary at a given time in the circulation to be visualized on the films. Therefore, minute shunts or minimal overriding of the vessels will be overlooked by this method. b. Certain chambers or portions of chambers may be opacified for only a fraction of the cardiac cycle. Therefore, the speed and frequency of exposure become exceedingly important. The minimum practical requirement for a serialographic machine appears to be 10 to 12 films in eight seconds, although there

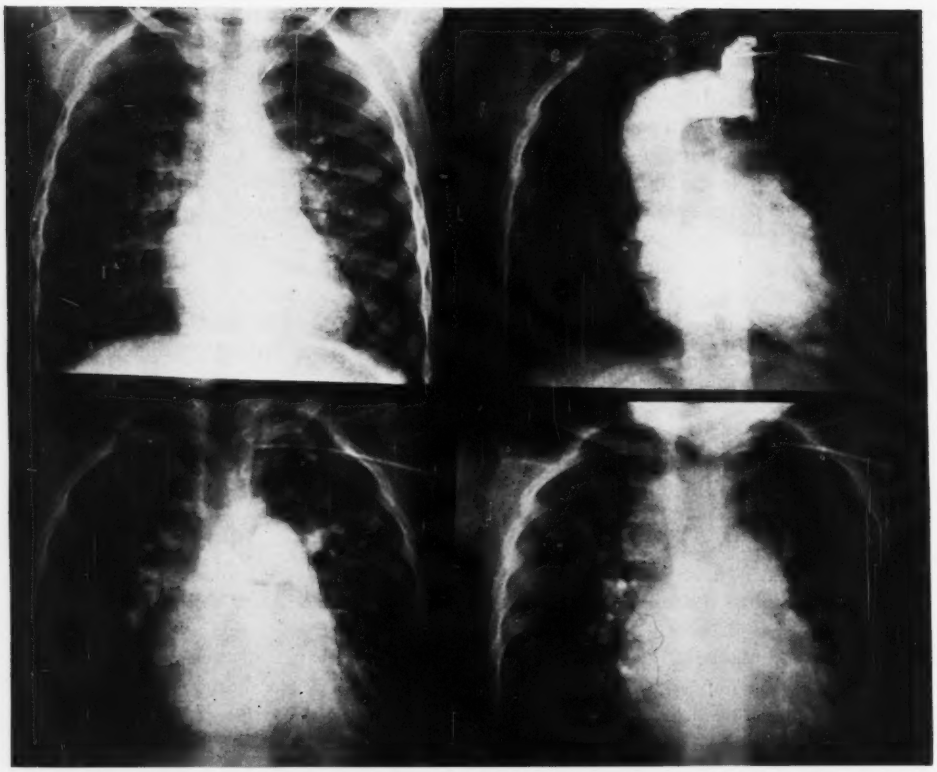


FIG. 9. Anomalous pulmonary venous return with complete drainage of pulmonary blood into the right side of the heart via a persistent left-sided vena cava draining into the innominate vein and then into right vena cava resulting in the "figure of 8" configuration of the mediastinum.

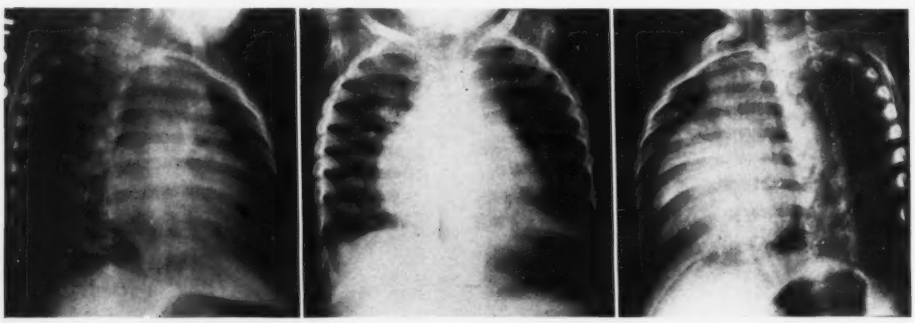


FIG. 10. Anomalous pulmonary venous return with only slight widening of the upper mediastinum on the left resulting from abnormal venous return but with marked enlargement of the right atrium resulting from the direct return of the major portion of the pulmonary blood into the right atrium.

appears to be some evidence that a faster rate of exposure may yield additional significant information.[19]

The literature is studded with reports in which angiocardiography either failed to give information or was actually misleading.[10, 51, 57,] As a rule, angiocardiography may show right-to-left intracardiac shunts of moderate magni-

ude, while left-to-right intracardiac shunts re better demonstrated by the catheter. There as been an increased application of angiocardiography in the diagnosis of lesions in the eonatal period and infancy. Here, in the pinion of the authors, this diagnostic instrument has unique rewards to offer, in that it is possible to follow the course of the blood and o establish abnormalities prior to the time hat adaptive changes take place in the heart which might make them recognizable by routine methods. This becomes important clinically in those infants suffering cardiac enlargement, failure, or other gross cardiac disturbances which cannot be diagnosed by other means.[59]

Retrograde Aortography

This specialized surgical procedure yields specific information in the localization of left-to-right shunts, in establishing whether they are intracardiac or extracardiac. This is a problem in which the catheter has not proved to be entirely accurate, and one which arises primarily in differentiating the inoperable high interventricular septal defects from the operable aortic-pulmonic defects and the patent ductus arteriosus. In coarctation of the aorta this procedure may yield specific information regarding the location of the coarcted segment. The retrograde injected dye follows the course of the blood instead of piling up above and below the coarcted segment, so that, as a rule, it demonstrates the entire collateral vascular channels better than the coarctation itself. The tighter the coarctation becomes, the more difficult it is to outline it accurately by dye.

This procedure should not be treated lightly, s deaths and cerebral complications are known o occur with considerable frequency,[60] apparntly the result of a high concentration of the ontrast material reaching the brain. Complicaions probably can be minimized by checking he position of the catheter fluoroscopically rior to injection, if a catheter is used, to be ertain that it has not passed up the carotid, y compression of the head and neck vessels ephalad to the site of the injection, and by voidance of multiple injections.

Vascular Rings and Aberrant Vessels

There are many vascular malformations of the aortic arch and its branches, but the majority are of little importance. Those which produce actual compression of the trachea or the esophagus or both may give rise to difficulties in swallowing and stridor. The symptoms in these cases are almost invariably exaggerated during feeding. Fortunately, these anomalies can be readily recognized by roentgenoscopic and roentgenologic examination. Our cases have fallen into two general categories, the compression produced by complete vascular ring and compression by a single malplaced or aberrant artery. In the double aortic arch, the trachea and esophagus are trapped between the arches, one arch passing anterior to the trachea, the other posterior to the esophagus. This deformity produces a characteristic roentgenologic appearance.[61] Another form of ring is produced by the right aortic arch with a persistent ligamentum arteriosum passing posterior to the esophagus and connecting with the pulmonary artery, similarly compressing the trachea and esophagus, but producing a somewhat different roentgenographic appearance. Fortunately, both of these deformities are amenable to surgery.

A single anomalous artery may also produce compression deformities with symptoms. The anomalous innominate artery may arise further along on the aortic arch than normal and, thus, wind around the anterior surface of the trachea, compressing it. The symptoms are usually dyspnea, stridor, and multiple bouts of pneumonia.

The aberrant subclavian artery is usually the result of the right subclavian taking off independently from the distal part of the aortic arch rather than from its normal origin, the innominate. Then, in order to ascend to the right upper part of the chest, it must pass either between the trachea and esophagus, anterior to the trachea, or behind the esophagus, the latter being by far the most common course. In doing so, it produces a spiral defect in the posterior and left lateral aspect of the esophagus, often associated with obstructive symptoms and long known as the cause of so-

called "dysphagia lusoria." This deformity is readily recognizable by barium swallow, and in infants there may be a temporary delay with momentary expansion of the upper part of the esophagus as a result of this deformity, particularly when solid or semisolid foods are taken. This often results in gagging and in distress during feeding and, at times, aspiration, although at no time has the obstruction been observed to be severe. In our series of aortic arch anomalies we have had approximately 40 patients within the past five years with symptoms sufficiently severe to justify surgical correction.[62]

Conclusion

As the scope of surgical corrective procedures for congenital heart disease widens, the burden of accurate diagnosis mounts. Correlation of all available data, not just roentgenographic, is the *sine qua non* for an understanding of the various types of congenital heart disease.

In our present state of knowledge, the simpler diagnostic procedures: History, physical examination, electrocardiogram, film and fluoroscopic observations, if properly correlated, should yield a working physiological diagnosis in 85 per cent of patients with congenital heart disease. The exact nature of the lesion in half of the remaining 15 per cent may become clear after angiocardiography and/or catheter studies.

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CLINICAL CONFERENCE

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Primary Arteritis of the Aortic Arch

By NELSON W. BARKER, M.D. AND JESSE E. EDWARDS, M.D.

THE following case is reported because of some unusual clinical and pathologic features and in order to call attention, first, to the aortic-arch syndrome in general and, second, to the rather uncommon primary arteritis of the aortic arch and its major branches which has been the subject of some previous isolated reports in the medical literature.

A housewife aged 64 years and the mother of four children was admitted to the hospital on Feb. 12, 1953, because of dyspnea and substernal pain that extended into the neck. She said that her health had been failing for approximately a year, during which time she had noted increasing fatigue, anorexia, gradual weight loss of 10 pounds (4.5 Kg.), and vague pains in the right side of the thorax. At the onset a year previously, she had had an episode of moderate substernal pain that seemed to localize finally in the interscapular region and lasted several days. For two months prior to admission to the hospital she had episodes of rather severe substernal pain and dyspnea on exertion, and these attacks had become more frequent, more prolonged and more easily induced. None of the episodes had lasted more than 30 minutes and all had been relieved by rest.

The past history revealed that the patient had stopped menstruating at the age of 41. She had consulted the Mayo Clinic in 1947 and 1951 about varicose veins and a cystocele but had received no definitive treatment for these conditions. In 1951 the plasma lipids had been determined, and the values were 150 mg. for cholesterol, 190 mg. for phospholipids and 349 mg. for total lipids, all per 100 cc. of plasma. The father had died of pulmonary tuberculosis at the age of 54 and the mother had died of hypertension and a "stroke" at the age of 82; otherwise the family history was not remarkable.

On admission the patient appeared to be seriously ill. She was rather thin, pale, nervous and apprehensive. Her temperature was 100.2 F. The thyroid was small, rather firm and slightly irregular, especially in the right lobe. The heart appeared to be normal in size; there was a regular tachycardia with an apical rate of 144 beats per minute, and there was a moderate systolic murmur heard only at the apex. Pulsations were palpable and were of normal volume in both carotid arteries, in the right subclavian artery above the clavicle, in the abdominal aorta, in both femoral arteries in the groins, and in both popliteal and both posterior tibial arteries. Pulsations were palpable but of reduced volume in both dorsalis pedis arteries. No pulsations could be felt in the left subclavian artery above the clavicle nor in the axillary, brachial, antecubital, radial and ulnar arteries of either arm. Blood-pressure readings were not obtainable in either arm. The blood pressure in the left lower extremity with the cuff around the thigh was recorded as 180 mm. Hg systolic and 90 mm. diastolic, and similarly in the right lower extremity as 140/90. The remainder of the examination gave negative results. There was no cyanosis, the lungs were clear and both hands were warm and of normal color. There was no swelling or edema of the extremities and there was no evidence of enlargement of the liver.

The urinalysis disclosed albuminuria, graded 4 plus, and the presence of a few hyaline casts and a few leukocytes. The value for hemoglobin was 11.4 Gm. per 100 cc. of blood and the erythrocytes numbered 4,130,000 and the leukocytes 4,600 per cubic millimeter. The sedimentation rate was 75 mm. in 1 hour. The value for blood urea was 50 mg. per 100 cc. Roentgenographic examination of the thorax showed evidence of a small amount of fluid and pleural thickening at the right costophrenic angle and slight torsion but no real dilatation of the aorta. The electrocardiogram showed a cardiac rate of 150 beats per minute, sinus tachycardia, left axis deviation, inverted T waves in leads I and II, depressed S-T segment in leads I, II and III. R waves were absent in leads V_1, V_2 and V_3. T waves were inverted in leads V_4, V_5 and V_6. S-T segments were elevated in leads V_1 and V_2 and markedly depressed in leads V_4, V_5 and V_6.

During her course in the hospital the patient continued to be dyspneic and became orthopneic. On the day following admission she seemed to feel better, was less apprehensive and had no distress in the thorax. Her temperature remained normal most of the day. She still appeared pale and the tachycardia continued. Forty-eight hours after admission

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the apical rate was still 150, there was evidence of gallop rhythm and more dyspnea, and there were moist rales in the bases of both lungs, particularly in the left. In the afternoon of that day, February 1, her temperature and pulse rate rose progressively, her dyspnea increased, and she became cyanotic, then comatose, and died.

From the clinical standpoint it seemed obvious that this patient entered the hospital with severe heart failure and pain that was strongly suggestive of myocardial ischemia. The onset of the pain had been somewhat gradual and its severity had been progressive. There had been no prolonged episode of pain, such as commonly occurs in coronary occlusion with myocardial infarction. The electrocardiogram gave strong evidence of severe myocardial ischemia or subendocardial anterolateral myocardial infarction, and the clinical course suggested the progressive failure of severe acute myocardial infarction. The more interesting and unusual finding was the lack of pulsations in the arteries of both arms including the left subclavian above the clavicle, but not the right subclavian, without evidence of severe or symptomatic ischemia of the arms and hands. This was indicative of localized occlusion of the left subclavian artery near its orifice and of the right axillary artery.

The first clinical impression was that the patient had coronary atherosclerosis with thrombosis, acute myocardial infarction with intracardiac thrombosis and embolic occlusion of the left subclavian and right axillary arteries. However, it was admitted that embolic occlusion of the large arteries of both upper extremities was an unusual occurrence and that there had been no sharp episodes of acute ischemia of either arm suggestive of embolic occlusion.

It was then suggested that the patient had atherosclerotic occlusion of the coronary artery, the left subclavian and the right axillary arteries. It is not unusual to see orificial atheromatous occlusion of the left subclavian artery both with and without evidence of coronary atherosclerosis, but it is very unusual to see associated or independent atherosclerotic occlusion in the right axillary artery or even in the right innominate artery. Furthermore, it was thought that the low values for plasma lipids noted in 1951 would be somewhat unusual in a woman of her age who had advanced atherosclerosis.

It was considered that the patient might have thyrotoxicosis, causing myocardial failure, secondary intracardiac thrombosis and embolization of the arteries of the upper extremities. This would have been compatible with the general deterioration of health, loss of weight, marked tachycardia and low values for plasma lipids. However, by palpation the thyroid gland did not seem to be definitely abnormal, auricular fibrillation was not present at any time and the electrocardiogram certainly indicated myocardial infarction rather than thyrotoxicosis. The dyspnea and serious clinical condition precluded a satisfactory determination of the basal metabolic rate; determinations of protein-bound iodine were scheduled but death occurred before they could be made.

Dissecting aneurysm was considered but such a lesion was thought not to be compatible with the transient character of the attacks of pain, the electrocardiographic findings and the occlusion of only one of the branches of the aortic arch near its orifice.

Thromboangiitis obliterans was ruled out in the diagnosis because of its rarity among women and among persons of either sex in the seventh decade of life, because of the extreme rarity of primary involvement of the coronary arteries by this disease, and because of its predilection to affect the more distal rather than the proximal arteries and the arteries in the lower as well as the upper extremities when the latter are involved at all.

Syphilitic aortitis with involvement of both coronary and subclavian arteries was considered. Cases of the so-called aortic-arch syndrome caused by syphilitic aortitis have been reported, but in the present case there was no history of syphilis, the serologic reaction for syphilis was negative, and there were no other signs, clinical or roentgenologic, indicative of syphilitic aortitis.

The curious type of aortic-arch syndrome which has been called "pulseless disease,"

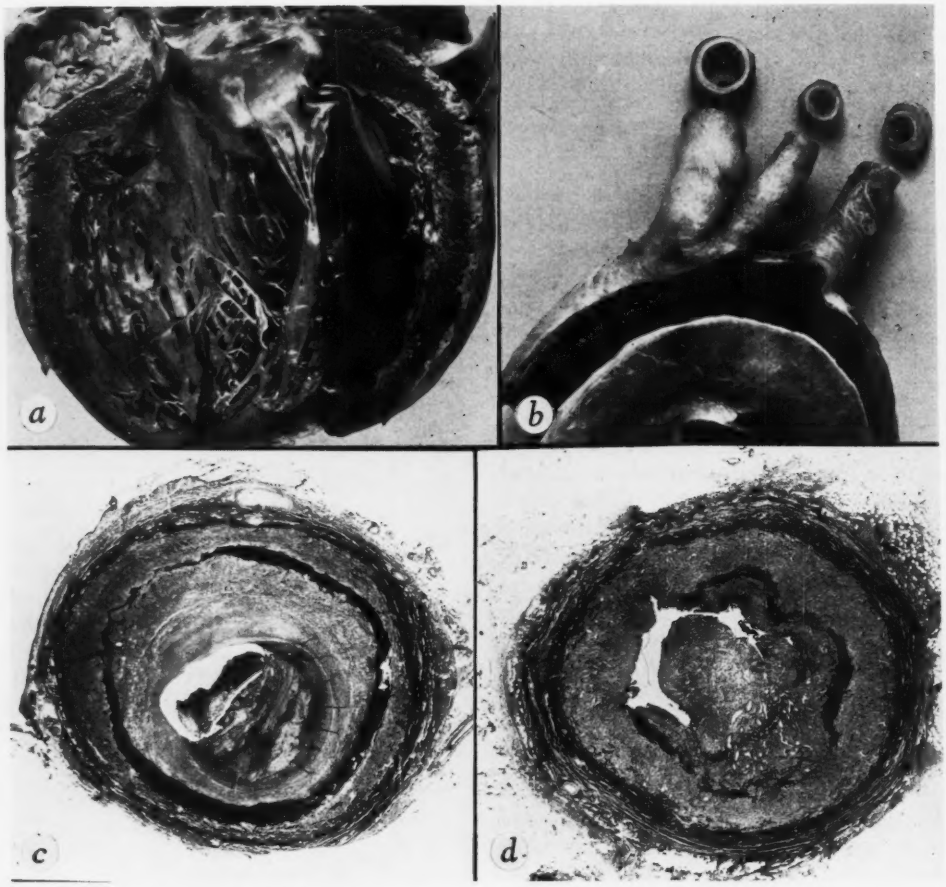


FIG. 1*a*. Left ventricle. Thinning of wall associated with acute infarction involving the anteroseptal and lateral regions. A mural thrombus is present in the left ventricle. 1*b*. Aortic arch and branches. The wall of each is thickened, and an organizing thrombus occludes the lumen of the left subclavian artery. 1*c*. Left subclavian artery. The narrowed lumen is filled with an organizing thrombus. There is intimal thickening with fibrous tissue. Much of the medial elastic tissue has disappeared. There is thickening of the media due to heavy cellular infiltration similar to that illustrated in figure 2*a* (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×8). 1*d*. Right axillary artery. The lumen is occluded by an organized thrombus. There is considerable loss of medial elastic tissue (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×12).

"young female arteritis" and "Takayasu's disease," and which has been the subject of isolated reports in the literature, remained for consideration. Unfavorable to such a diagnosis in the present case, however, were the fact that all reported cases have been in young women and the fact that the clinical findings have usually indicated occlusion of both arteries of the upper extremities and both carotid arteries.

Pathologic Examination. Necropsy revealed slight cardiac enlargement and acute subendocardial myocardial infarction involving the anterior and adjacent septal and lateral portions of the left ventricle (fig. 1*a*). A mural thrombus was present over the infarct and another in the left auricular appendage. The coronary arteries throughout their course showed no significant atheromatous disease or other type of narrowing except at the ostia. The ostia of both coronary arteries, but more strikingly the left, were narrowed considerably, the left ostium measuring only about 2 mm., the right about 3 mm., i

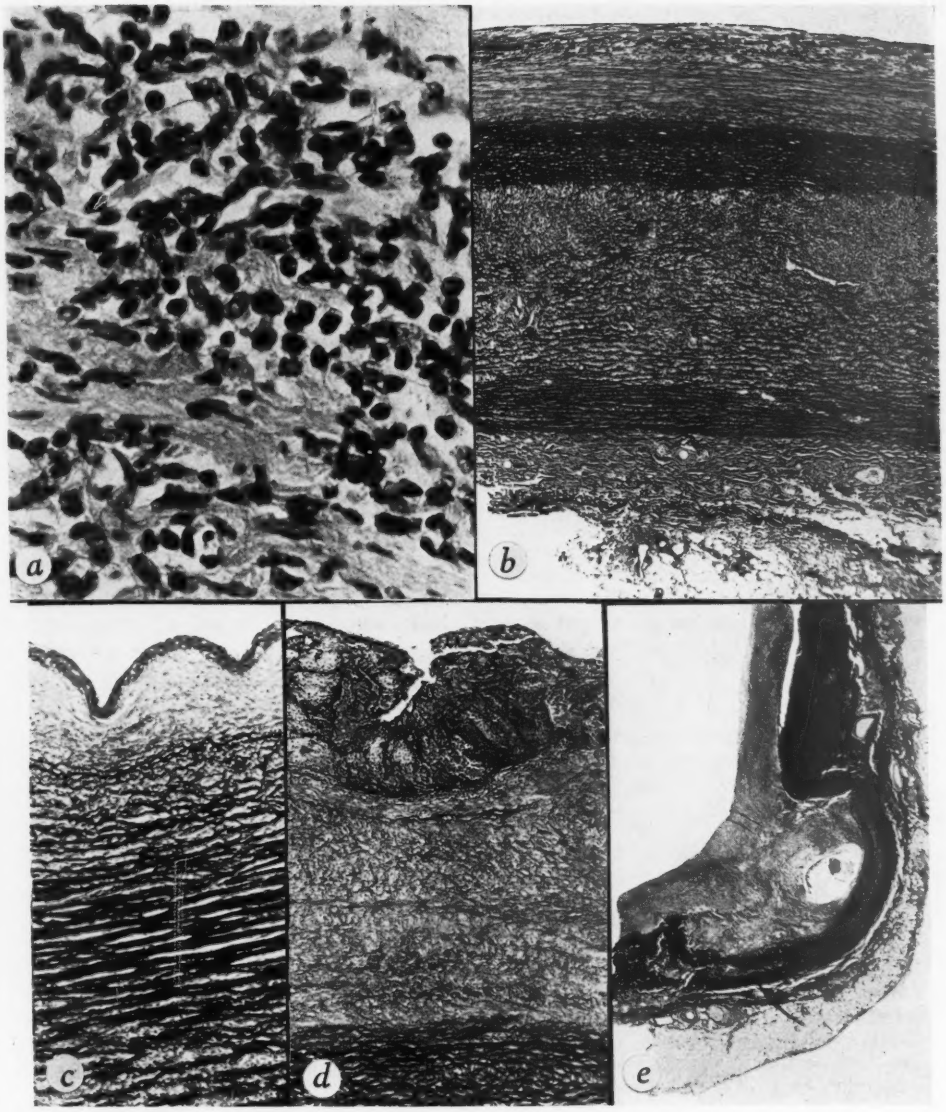


FIG. 2*a*. Media of innominate artery showing separation of elements by heavy cellular infiltrate composed mainly of macrophages and lymphocytes (hematoxylin and eosin; ×600). 2*b*. Thoracic aorta showing nonatheromatous fibrous thickening of intima (top of illustration). The central half of the media is pale because of loss of elastic fibers and separation of existing ones by infiltrating cells similar to those observed in the innominate artery and illustrated in *a* (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×30). 2*c*. Innominate artery. Fibrous nonatheromatous thickening of the intima. On the intimal surface there is fibrin undergoing organization. Medial elements are separated by infiltrating cells (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×90). 2*d*. Thoracic aorta. Pronounced intimal nonatheromatous fibrous thickening (center of illustration). On the surface of the intima there is a heavy layer of thrombus (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×50). 2*e*. Longitudinal section of aorta through ostium of left coronary artery. Pronounced intimal thickening of the aorta involves the ostium of the coronary artery causing narrowing of the latter (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain; ×10).

diameter. The thoracic aorta in its entirety had a peculiar, leathery, thickened quality. There were no localized lesions in any portion of the thoracic aortic wall.

As to the branches of the aortic arch, the lumen of the left subclavian artery was occluded by an organizing thrombus, beginning at the origin of the vessel and continuing for a distance of about 2 cm. from that point (fig. 1*b* and 1*c*). The walls of the left common carotid and the innominate arteries were thickened, but the lumens were patent. While the right subclavian artery had a patent lumen, the right axillary artery was occluded by an organized thrombus (fig. 1*d*). There were minimal calcific changes in the leaflets of the aortic valve, but no stenosis. Considerable central hemorrhagic necrosis was present in the liver. There was considerable edema of the lungs, the combined weight being 1,410 Gm. Minimal hydrothorax existed—500 cc. of fluid on the right and 350 cc. on the left. Recent infarcts considered to be the result of emboli from the cardiac mural thrombi were present in the kidneys. Colloid adenomas were present in the thyroid gland.

Histologic examination revealed the myocardial infarct to be recent, and its appearance was compatible with the concept that it had originated three days before death. No evidence of inflammation save that related to the myocardial infarction was present in the heart.

The entire thoracic aorta and the branches of its arch, as well as the axillary arteries, were characterized by an extensive chronic inflammatory reaction (figs. 1*c*, 1*d* and 2). This was most striking in the medial layer of the involved vessels, where there was heavy infiltration with cells, for the most part macrophages and lymphocytes (fig. 2*a*). In some areas the infiltrating cells caused the spaces between the elastic fibers of the media to be widened. In still other areas there was interruption of elastic fibers (figs. 1*c*, 1*d*, 2*a* and 2*b*). In such areas there were wide gaps of the media, in which no pre-existing elements but only loose connective tissue containing the infiltrating cells was identifiable. No giant cells were found and neutrophils did not take noticeable part in the cellular reaction. While some increase in vascularity of the media occurred, there was no scarring. No bacteria were seen. Related to the medial inflammatory process there was fibrous nonatheromatous thickening of the intima of the aorta and the branches named (fig. 2*c*, 2*d* and 2*e*). Minimal cellular infiltration occurred in some foci at the junction of the media and intima, but this was not a striking feature. An organizing thrombus in the left subclavian and an organized one in the right axillary artery completely filled the respective lumens (fig. 1*c* and *d*). In the left common carotid, the innominate artery and the aorta, there were mural thrombi which were undergoing organization (fig. 2*c* and 2*d*).

The coronary arteries distal to the ostia showed little or no atheromatous change and nowhere were they involved by inflammatory changes similar to those seen in the aortic arch and its branches. In the case of the left coronary artery a longitudinal section of the aortic wall extending into the left coronary artery was made. This showed that the aortic media here was characterized by the same inflammatory process that characterized the media of the thoracic aorta elsewhere. Likewise, as elsewhere, the intima of the aorta was thickened by nonatheromatous connective tissue, which involved the site of origin of the left coronary artery and caused the ostium of that vessel to be narrowed (fig. 2*e*). In the left coronary artery, only minor infiltration of the vessel as it was related to the aortic wall was present.

A section of the pulmonary trunk revealed no inflammatory process.

Comment

The somewhat unusual clinical picture in this case may be brought together by the necropsy findings. The cardiac murmur which had been noted for several years could be explained on the basis of minor changes in the aortic valve of a fibrocalcific nature which did not seem to contribute to cardiac dysfunction. The history of angina could readily be correlated with the existence of narrowed coronary ostia. This feature was the expression of the fibrous intimal thickening of the aorta as part of the disease described in that vessel. No thrombotic or other form of acute occlusion of the coronary arteries was found. The fact that the myocardial infarct involved the endocardial half rather than the entire thickness of the myocardium is consistent with everyday observation of the tendency for myocardial infarcts occurring in the absence of acute coronary occlusion to be subendocardial in distribution. The mural thrombi of the left ventricle and of the left atrium are interpreted as manifestations of cardiac failure resulting from the myocardial infarction involving an extensive portion of the heart. Other expressions of cardiac failure are to be had in the central hemorrhagic necrosis of the liver, the hydrothorax and the pulmonary edema.

In the presence of intracardiac thrombi one naturally wonders whether the thrombi occluding the left subclavian and right axillary arteries could have been embolic. The evidence is against this and favors thrombosis *in situ*.

The ages of the arterial thrombi were greater than the age of either the myocardial infarction or the complicating intracardiac mural thrombi. Additional evidence supporting the view that the occlusions of the arteries were thrombotic comes from the fact that mural thrombi were found widely distributed in the thoracic aorta and in the left common carotid and innominate arteries. The thrombosis is interpreted as a direct complication and accompaniment of the arteritis and aortitis. The renal infarction was fresh and probably resulted from emboli originating in the heart.

The sequence of events indicates that the patient's illness and death were ultimately related to aortitis and arteritis. Nevertheless, the cause of the arterial disease remains obscure.

One is led to consider syphilis as a cause of the arteritis. The results of clinical tests in this case were negative for this disease. The lack of scarring of the media is evidence against a diagnosis of chronic syphilitic aortitis, and the lack of giant cells in the very heavy medial cellular infiltrate is evidence against a diagnosis of acute syphilis.

Although this patient was a woman and so was not potentially a ready subject for thromboangiitis obliterans, that condition comes up for consideration. Against it are the clinical features of involvement of the upper extremities to the exclusion of the lower. In thromboangiitis obliterans the classic granulomatous picture with giant cells is not always seen. At certain stages, when cellular infiltration is as heavy as it was in this case, there is usually giant cell infiltration, but no such cells were present here. There was no evidence of involvement of veins nor of extensive fibrosis in the connective tissue supporting the arteries, veins and nerves. The typical picture of panangiitis of thromboangiitis was not seen. Although thromboangiitis obliterans should be mentioned in the differential diagnosis, the evidence does not strongly favor such a diagnosis.

The case presented seems to represent a condition which has previously been described, mentioned in some reviews, and at times referred to as "pulseless disease" and "Takayasu's disease." This condition, while observed in both sexes, has shown a great tendency to occur in women, according to reports in the literature. In their review of various conditions related to disturbances of the aortic arch and its branches, Ross and McKusick[1] referred to this condition as "young female arteritis." The present case fulfills the clinical and pathologic criteria of this condition except in respect to the patient's age.

The case presented brings up for discussion the term "reverse coarctation," since there was absence of pulsation in the arms with evidence of normal pulsation in the abdominal aorta and femoral arteries. Usually this term is applied to cases in which the branches of the aortic arch are obstructed but in which there is evidence of unimpeded flow of blood to the lower part of the body. In the case presented, the carotid arteries pulsated normally and, although the right radial pulse was absent, the right subclavian artery pulsated normally, the obstruction being in the right axillary artery.

Under these circumstances the term "reverse coarctation" would not be applicable, since it signifies that there is evidence of arterial obstruction to all the branches of the aortic arch. In passing, it may be mentioned, however, that so-called reverse coarctation is essentially the result of acquired disease of the aorta. At times there may be associated variants whereby the branches of the aortic arch arise in an abnormal manner, but the underlying cause of the obstructive phenomena does not reside in such developmental deviations, if present. The most common condition giving rise to the phenomenon of "reverse coarctation" is syphilitic aortitis, in which the branches of the aortic arch are obstructed in one way or another. They may be obstructed because the process involving the aortic wall narrows the ostia of these vessels, or thrombosis may cause the vessels to be obstructed. The thrombus may be within the branches. More commonly, however, when there is evidence of obstruction to the three branches of the arch there is an associated aneurysmal formation of the aortic arch complicated by mural thrombosis at this site.

Other forms of aortic aneurysm associated with thrombosis such as arteriosclerotic aneu-

rysms or aneurysms resulting from trauma may account for the phenomenon of "reverse coaretation," but these are much less common than syphilitic aortitis.

It will be recalled that in the present case coronary insufficiency with myocardial infarction played a prominent role in the symptomatology and was actually the cause of death. This circumstance is unusual among patients having the type of arterial disease present here. According to the review of Ross and McKusick,[1] the most common symptomatology reflects the obstruction to the carotid arteries, when present. In our case the coronary insufficiency should be attributed not to intrinsic coronary arterial disease, but rather to the aortitis. It will be recalled that one feature of the aortitis was pronounced fibrous intimal thickening which coincidentally caused narrowing of the coronary arterial ostia. In this way there was significant anatomic obstruction to coronary flow in the presence of intrinsically normal coronary arteries.

REFERENCE

[1] Ross, R. S. and McKusick, V. A.: Aortic arch syndromes: Diminished or absent pulses in arteries arising from arch of aorta. A.M.A. Arch. Int. Med. **92:** 701–740, 1953.

ABSTRACTS

BLOOD COAGULATION

Wessler, S. and Fischbein, J. W.: An Improved Method for the Intravenous Administration of Heparin. Its Clinical Application. New England J. Med. **250:** 860 (May 20), 1954.

A method is described for intravenous administration of heparin which avoids repeated venipunctures. An inlying polyethylene catheter, 15 cm. long, is used, its distal end fitted with a rubber-capped Tuohy-Borst adapter. This technic was employed for intravenous administration of heparin in 38 patients with a variety of thrombotic and thromboembolic disorders. Seven patients with acute myocardial infarction were also treated. In none of the patients was superficial or deep thrombophlebitis, embolism, fever or septicemia from the catheter encountered. Cultural studies of the catheters at the time of their removal disclosed no evidence of contamination. In less than one-quarter of the patients there was a slight localized reaction to the polyethylene tubing. Catheters remained in the veins for from one to four weeks. It is pointed out that this technic may be useful in many types of intravenous therapy and for obtaining multiple blood samples without recourse to repeated venipunctures.

ROSENBAUM

Brown, K. W. G. and MacMillam, R. L.: The Choice of An Anticoagulant. Am. J. M. Sc. **227:** 526 (May), 1954.

A group of patients suspected of having thromboembolic disorders were given one of the four anticoagulant drugs under study in order to determine their relative effectiveness and hazards. The preparations included heparin given intramuscularly, Dicumarol, Phenylindanedione, and Cyclocumarol. All four anticoagulants were equally effective in the prevention of further thromboembolic complications. Significant bleeding occurred in 5.7 per cent of patients. Heparin produced the highest incidence of bleeding and was frequently associated with pain at the site of injection. It is stated that heparin should be reserved for rapid initiation of anticoagulant therapy. Agranulocytosis developed in 2 patients who received phenylindanedione. On the basis of their study, the authors believe that Dicumarol is the most satisfactory preparation for anticoagulant therapy.

SHUMAN

Penn, S. R. and Walker, J. H.: Defective Blood Coagulation Following Pulmonary Surgery. New England J. Med. **250:** 764 (May 6), 1954.

Two cases of severe hemorrhage are reported supposedly due to blood coagulation defects developing following pulmonary resection for bronchiectasis. In one case the defect was not recognized and the patient died following a secondary exploration at which no bleeding point was found. The coagulation defect was recognized in the second patient and intravenous administration of fibrinogen was followed by recovery. It is mentioned that Stefanini has regarded fibrinolysis responsible for bleeding more frequently than is commonly recognized and that kinases which are abundant in the uterus and lung may activate fibrinolysis *in vivo* if they enter the circulation. Defects in blood coagulation may appear even though preoperative studies may have been normal; postoperative study of the blood clotting time and of the clot itself is indicated in determining the cause of the bleeding.

ROSENBAUM

CONGENITAL AND RHEUMATIC DISEASE

Kroeker, E. J., Kirkin, J. W., Prickman, L. E., and Wood, E. H.: Coarctation of the Aorta, Subaortic Stenosis; Anomalous Right Subclavian Artery. Proc. Staff Meet. Mayo Clinic, **29**: 266 (May), 1954.

Pressures were measured directly and dye dilution curves were recorded from both radial arteries and the right femoral artery before and after surgical correction of a coarctation of the aorta in a 38 year old man with an associated subaortic stenosis and moderate stenosis of the right subclavian artery, which originated distal to the coarctation. Before operation, pressure in the left arm was moderately elevated, pressure in the femoral arteries was reduced while an intermediate pressure and pulse contour was present in the right radial artery. These conditions were restored toward normal following the operation.

The right and left radial artery pressures and electrocardiogram were recorded throughout the operation and the effects of occluding the right subclavian artery, occluding the left subclavian artery and opening the completed aortic anastomosis were studied. It was demonstrated that blood flow in the anomalously arising right subclavian artery at its origin was from the subclavian into the thoracic aorta instead of in the normal distal direction, and that except for the coronary and cephalic circulations, the major and practically only source of blood supply for the remainder of the body was via the left subclavian artery.

SIMON

Wilburne, M., and Mack, E. G.: Paroxysmal Tachycardia in the Newborn With Onset in Utero. J.A.M.A. **154**: 1337 (April 17), 1954.

This case of congenital paroxysmal supraventricular tachycardia with a rate of 312 per minute brings to 12 the total number of reported cases of all forms of prenatal or congenital paroxysmal rapid heart action. After delivery the female child was promptly placed in oxygen because of cyanosis and obvious respiratory distress. It was estimated that her heart rate was above 280 per minute immediately after birth. On tincture of digitalis, the tachycardia was replaced three and one-half days later by normal sinus rhythm at the rate of 128 per minute. When the baby was six weeks old the tachycardia recurred. At this time an electrocardiogram revealed supraventricular tachycardia with a rate of 312 beats per minute. She was given tincture of digitalis but on the following day dependent edema developed and the baby was given lanatoside C 0.1 mg. intramuscularly. One hour later 0.25 mg. was administered intramuscularly, and 6 hours later 0.4 mg. was given the same way. Eight hours later normal sinus rhythm at the rate of 130 beats per minute was noted. The child was put on maintenance doses of tincture of digitalis for one month after which the dosage was reduced to a minim every two days. When the baby was three and one-half months old, the paroxysmal tachycardia again developed. An increase in digitalis tincture dosage caused the rhythm to revert to normal sinus. At age seven and one-half months the digitalis maintenance dose was discontinued. The child now is 15 months old and in normal health.

KITCHELL

Wood, P.: An Appreciation of Mitral Stenosis. Part I. Clinical Features. Brit. Med. J. **1**: 1051 (May 8), 1954.

The author reports observations on about 300 cases, about half of which were submitted to operation. The methods of evaluation were those used in many other studies which have been or are being reported. The author grades "all symptoms, measurements, and graphic patterns . . . from 0 (absent) to 4, the four positive grades representing the common English adjectives of degree slight moderate, considerable, and gross". Wood proposes that the relative incidence of involvement of the several valves may be related to the relative pressure load at which they operate. In the child of the age at which rheumatic damage is occurring this is of the order of 100, 60, 15, and 6 mm. Hg, respectively, for mitral, aortic, tricuspid, and pulmonic valves.

Contrary to the usual concepts 78 per cent of patients with "a really high pulmonary vascular resistance" had never passed through a stage of orthopnea or paroxysmal dyspnea. Angina pectoris indistinguishable from that associated with occlusive coronary atherosclerosis was encountered in 12 per cent of the cases submitted to surgery and in 3 per cent of the cases of "almost pure mitral incompetence." Angina disappeared after "technically successful valvotomy." Following exercise ischemic depression of ST segments in the left ventricular surface leads or their equivalent developed. Occurrence of angina correlated well with the size of the mitral orifice. Although there was also a direct correlation with the degree of elevation of pulmonary vascular resistance, Wood believes that angina in mitral stenosis is the result of limitation of cardiac output and that the left ventricle suffers most

A history of systemic embolism was obtained in 13 per cent of the whole series (14 per cent of those cases submitted to operation). Embolism occurred at operation in 10 per cent of the cases. This accident was not significantly higher in those patients with a history of previous embolism. The surgeon found clots in the left atrium no more frequently in patients with a history of embolism than in others; this suggests that fresh clots are the ones which are likely to embolize.

With atrial fibrillation the first sound was most accentuated after a short diastolic interval. No case of significant mitral regurgitation as checked by the surgeon had grade 3 accentuation of the first heart sound. Extensive calcification was less likely to be

accompanied by marked accentuation of the first sound. There was a positive correlation between the intensity of the first sound and the presence and intensity of the opening snap. Normal rhythm favors accentuation of the first sound by increasing the pressure gradient across the mitral valve at the end of diastole.

A close correlation was found between the incidence and grading of the mitral systolic murmur and the presence and degree of regurgitation recognized by the surgeon at operation. In 16.5 per cent of the cases of mitral stenosis submitted to valvotomy an opening snap was absent. In 32 per cent of those cases with an opening snap, it disappeared after valvotomy. Half of these attained an excellent result, whereas conspicuous regurgitation was produced in the others. The opening snap is excellent evidence against the presence of serious mitral regurgitation. It may, however, be present with relatively trivial degrees of mitral obstruction.

Significant systemic hypertension occurred in about 10 per cent of the cases. The characteristic pulse of mitral regurgitation was of the small water-hammer type. These characteristics are attributed by the author to hyperdynamic ventricular systole in combination with low cardiac output. Giant *a* waves in the phlebogram indicated either extreme pulmonary hypertension or tricuspid stenosis. Left ventricular thrust at the apex beat and lift over the right ventricle were useful indices of hypertrophy of the left ventricle and the right ventricle, respectively.

In the cases with sinus rhythm a presystolic murmur was absent in all cases classed as pure mitral regurgitation and in one-third of the cases with serious degrees of regurgitation in combination with stenosis. A presystolic murmur is no evidence of the degree of mitral stenosis since it occurred even in the most trivial obstruction. The presystolic murmur persisted after operation in 42 per cent of the cases. Excluding those cases in which its disappearance could be attributed to the creation of mitral regurgitation by operation, 90 per cent of those showing disappearance had excellent results from operation.

In 85 per cent of the patients with well-developed mitral regurgitation, a third heart sound was present. This is quite clearly related to the hyperdynamic state of the left ventricle with rapid filling. In general it is distinguished from an opening snap by its later position in time, by its lower pitched and longer characteristics and by the failure for this third sound to be transmitted to the left sternal border. The presence of a third heart sound is a relative contraindication to valvotomy. None of these patients who were operated on did well and three-fourths of them died.

The diastolic rumble was completely absent in one patient with very high pulmonary vascular resistance. Most of the surgically favorable cases had long murmurs occupying most of diastole.

McKusick

Goyette, E. M., Farinacci, C. J., Forsee, J. H. and Blake, H. A.: The Clinicopathologic Correlation of Lung Biopsies in Mitral Stenosis. Am. Heart J. **47:** 645 (May), 1954.

A wedge of pulmonary tissue from the lingula was resected at the time of mitral valvulotomy and examined in each of 15 consecutive patients with mitral stenosis as the only significant valve lesion. A control group of 10 autopsy cases without cardiac or pulmonary disease was also studied. Qualitative histologic study was made of both the alveolar and vascular tissues for the purpose of correlation with the clinical and laboratory findings.

The changes in the alveolar walls consisted of capillary dilatation, thickening of the capillary basement membrane, increase in the interstitial tissue, pericapillary edema, and a transition to cuboidal epithelium. The lesions in the pulmonary vessels consisted of intimal thickening, medial hypertrophy, and scarring with narrowed lumens. The most marked alveolar and vascular changes tended to occur in older patients who had had their disease for longer periods or in patients with advanced disease, right ventricular hypertrophy, radiologic evidence of pulmonary fibrosis or hemosiderosis, high pulmonary artery pressure, and increased total pulmonary and pulmonary arteriolar resistances. There were noteworthy exceptions to all clinical and laboratory features, none of which consistently correlated with the pathologic findings.

No single feature or group of features was completely reliable in determining the degree of pulmonary changes present prior to operation nor did the pulmonary changes as determined by lung biopsy necessarily predict the degree of benefit obtained from valvulotomy.

Maxwell

Keyes, J. W., and Lam, C. R.: Recurrence of Mitral Stenosis Following Commissurotomy. J.A.M.A. **155:** 247 (May 15), 1954.

This communication presents the report of a 29 year old man whose mitral leaflets remained adequately open for a year and a half after commissurotomy and then re-fused again producing mitral stenosis. A second operation produced the same dramatic clinical improvement as the first one. Although recurrence of mitral stenosis after a technically adequate operation on the valve is extremely rare, when it does occur the possibility of a second (or even a third) operation should not be overlooked.

Kitchell

Varnauskas, E. and Werkö, L.: Temporary Occlusion of Interatrial Septal Defect in Man. Scandinav. J. Clin. & Lab. Investigation, **6:** 51 (No. 1) 1954.

A special catheter has been devised with three channels, one ending at the tip and two at the sides with two special balloons placed on the catheter so

that they may be dilated separately through the two channels ending proximately. Each balloon may be inflated with 25 ml. fluid. The catheter is passed into the right auricle through the septal defect, the left auricle and out into a pulmonary vein. The distal balloon is then inflated with diodrast and the catheter withdrawn until the balloon rests against the edge of the septal defect. The proximal balloon is then inflated and the defect is thereby closed. In this way it is possible to study the effect of exercise and drugs with the defect closed, and to register the left auricular pressure with the defect open or closed. To determine the cardiac output, a second catheter is introduced into the pulmonary artery. The proximal balloon is deflated and as the distal balloon is being deflated, the catheter is slowly pulled upon slightly but constantly. The degree of inflation of the distal balloon when it slips through the septal defect permits determination of the size of the defect. This technique is said to permit closure of only fairly small, well defined septal defects. It is said to have been used without difficulty or subjective symptoms and with few complications.

ROSENBAUM

Storer, J., Lisan, P., Delmonico, J. E., and Bailey, C. P.: Physiopathological Concepts of Mitral Valvular Disease. J.A.M.A. **155:** 103 (May 8), 1954.

This study is based on 225 patients with rheumatic disease of the mitral valve who were classified into three categories. Group 1 comprises those patients with pure mitral stenosis. Group 2 constitutes the so-called mixed group with mitral regurgitation estimated at less than 10 cc. per ventricular systole. Group 3 is made up of those patients with pure mitral insufficiency where regurgitation was estimated to be in excess of 10 cc. per ventricular systole. Classification is made by a new method of measurement of regurgitation made by the surgeon at the time of operation by the sensation he receives on the tip of his gloved finger which is in the auricle at the time of operation. The authors state that in this method regurgitation is conveniently although very approximately estimated in cubic centimeters per ventricular systole. Fibrillation predisposes to thrombus formation while insufficiency impedes this in the cardiac chambers subjected to the regurgitant jet. Atrial fibrillation plus a stenotic mitral valve produce a relative stagnation of left atrial blood providing a mechanism helpful to blood coagulation. With a mitral valve regurgitation the agitation of the contents of the left atrium provided by the regurgitant stream gives little opportunity for the blood to coagulate in that chamber. It appears that insufficiency has a greater role in diminution of thrombus formation than does the character of the valve. In this series fibrillation was most frequent in the primarily regurgitant lesion. Information available regarding group 2 patients suggests that these patients would have exhibited purely stenotic lesions at surgery were it not for the appearance of calcification of the valve during the course of disease. Calcification does not always result in an element of regurgitation because 2 per cent of group 1 showed calcification with no insufficiency. There were 20 per cent with calcified valves in group 3 which would suggest there are other factors more important than calcification in the production of major insufficiency. It appears that the deposition of calcium in the stenotic lesion increases the opportunity for the valve to become incompetent while in the regurgitant lesion it may increase the severity of the insufficiency but does not seem to be responsible for the primary lesion. The two most significant features of group 2 were seen in the high incidence of valve calcification (76 per cent) and a relative increase in the number of men. It is felt that a part of the tendency for men with stenotic lesions to develop insufficiency is the more forceful action of the male heart in response to a greater work load. The dual threat during surgery offered by thrombotic material and valvular calcific deposits as a source of emboli is pointed out. Four cerebral emboli occurred during surgery in the 225 cases. Three of these cerebral emboli occurred in group 2 patients and although no proof is available it may be that calcium was the offending agent.

KITCHELL

Wright, J. L., Burchell, H. B., Kirklin, J. W., and Wood, E. H.: Congenital Displacement of the Tricuspid Valve (Ebstein's Malformation). Proc. Staff Meet. Mayo Clinic. **29:** 278 (May), 1954.

The surgical closure of a patent foramen ovale in the heart of an adult patient believed to have Ebstein's malformation of the tricuspid valve resulted in cure of the cyanosis, in alleviation of the patient's symptoms and in a great increase of his exercise tolerance. In certain selected cases of Ebstein's malformation in which the venous shunt is large and apparently a major factor in the patient's disability, surgical closure of the atrial septal defect may be considered as a worth-while palliative procedure.

SIMON

Fletcher, G., DuShane, J. W., Kirlin, J. W. and Wood, E. H.: Aortic-Pulmonary Septal Defect. Proc. Staff Meet. Mayo Clinic. **29:** 285 (May), 1954.

A case of aortic-pulmonary septal defect is presented. At cardiac catheterization, severe pulmonary hypertension and a bidirectional shunt of blood at the pulmonary artery level were demonstrated. Preferential flow of the right-to-left shunted blood to the descending aorta was demonstrated by simultaneous blood oxygen saturation studies and dye dilution curves from the right radial and femoral arteries. Such findings have previously been con

idered to be pathognomonic of patent ductus arteriosus associated with severe pulmonary hypertension. Pertinent roentgenographic findings which might have been given a clue to the correct diagnosis are discussed.

The onset of ventricular fibrillation and the effectiveness of cardiac massage and subsequent electric defibrillation in effecting recovery from ventricular fibrillation is demonstrated by means of continuous electrocardiographic and arterial pressure recordings. The feasibility of surgical division and closure of aortic septal defect in at least some cases is again demonstrated.

SIMON

January, L. E., Bedell, G. N. and Bateman, R. D.: Problems of Mitral Valve Disease. J.A.M.A **155:** 231 (May 15), 1954.

Mitral valve disease today is inseparably linked with the surgical treatment of mitral stenosis. However, this should not obscure the fact that in the final analysis the main concern still lies with the unsolved mysteries of rheumatic fever: the mitral problem will be resolved not by surgical technique but by increasing knowledge of the disease and the discovery of means for its specific treatment and prevention. In selecting patients for mitral commissurotomy the authors use a modification of the classification proposed by Harkins to separate patients into four groups extending from group I (the milder cases who do not need surgery) to group IV (consisting of the severely incapacitated and often bed-ridden patients). The authors feel that the group IV patients, although seriously and often terminally ill, may deserve operation because a few of them possibly could be benefited. Group IV patients need intensive preoperative measures designed to control cardiac failure. Although minor degrees of aortic stenosis, aortic regurgitation, or mitral regurgitation do not contraindicate operation, significant enlargement of the left ventricle is a contraindication. For examination it is necessary to use special techniques other than simple auscultation. These commonly include roentgenography, fluoroscopy, electrocardiography, cardiac catheterization, and occasionally electrokymography, phonocardiography and ballistocardiography. There is a great difficulty in demonstrating significant left ventricular enlargement in the presence of right ventricular enlargement by fluoroscopy or radiographic study. No single criterion is adequate for the preoperative recognition of a degree of mitral regurgitation sufficient to contraindicate valvotomy for mitral stenosis. However, the demonstration of definite left ventricular enlargement in physical examination, roentgenogram, fluoroscopy or electrocardiogram without concomitant aortic valvular disease, hypertension, or cardiac failure, coupled with an apical systolic murmur of grade III intensity or louder, is the most reliable combination. A combination of two or more of these presumptive signs suggests extreme conservatism in recommending exploratory cardiotomy. Cardiac catheterization is not routinely required in the evaluation of patients for surgery. The effects of surgical treatment on 71 patients (18 men and 53 women) between the ages of 19 and 56 years is discussed. Although each was carefully studied, in 7 instances there was failure to recognize the contraindicating degree of mitral regurgitation. The postoperative complications were not unusual and the surgical mortality was less than 5 per cent. It is pointed out that however excellent the result from mitral valvotomy, the patient still has mitral disease and requires continued medical supervision. There is no reason to believe that the operation will make it less necessary to recognize and adequately treat group A beta hemolytic streptococcic infections in these patients or that the risk of recurrence of rheumatic fever will be changed. The patient's and the physician's responsibility for the prophylaxis of subacute bacterial endocarditis or its early recognition or adequate treatment has not been ended.

KITCHELL

Gray, I. R.: Mitral Stenosis and Hypertension. Brit. Heart J. **16:** 165 (Apr.), 1954.

The blood pressure in 200 instances of rheumatic heart disease with mitral stenosis were measured and, as a control, 200 instances matched for age and sex in which uncomplicated peptic ulcer was diagnosed. Hypertension is regarded as an incidental finding of no great significance. There is no appreciable change in the life expectancy unless the hypertension is severe when it adds to the disability.

SOLOFF

Whitaker, W.: Total Pulmonary Venous Drainage through a Persistent Left Superior Vena Cava. Brit. Heart J. **16:** 177 (Apr.), 1954.

Six instances of total pulmonary venous drainage of the heart are described. The striking feature is a "cottage-loaf" shaped cardiovascular shadow formed by an ovoid upper mediastinal mass and an enlarged heart. The ovoid mass is produced on the left by a persistent left superior vena cava and on the right by the dilated right superior vena cava. This anomaly is compatible with survival to the third decade and may produce little disability. The individuals may have dyspnea on exertion and recurrent attacks of pulmonary infection. There may be slight cyanosis and early clubbing of the fingers. The systemic pressure is usually low. There may be a prominent left chest wall and the physical characteristics of right ventricular hypertrophy. P_2 is usually loud and split. A pulmonic systolic murmur widely distributed may be heard and a diastolic murmur either at the apex or base or in both regions. The electrocardiogram shows either right ventricular hypertrophy or right bundle branch block. Radiology

is specific. The pulmonary arteries are prominent and pulsate. The heart is enlarged, due predominantly to the right auricle and right ventricle. Angiocardiography which is not needed for diagnosis is more informative if done through the left arm when the catheter can be seen to enter the left innominate vein, a dilated right superior vena cava and a dilated right atrium. Retrograde filling of the mouth of the left superior vena cava is seen. The oxygen is fully saturated in the pulmonary vein and the left superior vena cava. Surgery, as yet, has not been successful and was not advised in any of these patients because the disability was not regarded as sufficiently severe.

SOLOFF

Scott, W. G., Simril, W. A. and Seaman, W. B.: Intracerebral Arteriovenous Malformations. Their Diagnosis and Angiographic Demonstration. Am. J. Roentgenol. **71:** 762 (May), 1954.

On the basis of symptoms and physical findings and cerebral angiograms, the authors conclude that intracerebral arteriovenous malformations are more common than previously believed. The malformations can probably be traced to abnormalities in embryologic development and they may result in intracerebral or subarachnoid hemorrhage. Generally the malformations are either arterial-angiomatous or result in arteriovenous fistula.

Cerebral angiography is indispensable in the diagnosis. Ligation of main feeding arteries or of the internal carotid artery has on the whole been disappointing. Surgical extirpation or even radiotherapy seem to be preferable in selected cases.

SCHWEDEL

CONGESTIVE HEART FAILURE

Fejfar, Z. and Brod, J.: The Mechanism of General Haemodynamic Changes in Heart Failure. Acta med. Scandinav. **148:** 247 (Fasc. 4), 1954.

The character of the general hemodynamic changes in heart failure was studied in 17 patients with heart disease in various stages of congestive failure and in 5 normal controls by means of detailed observations of the cardiovascular hemodynamics before and after intravenous infusion of Dibenamine in doses of 3 to 10 mg. per kg. body weight in 100 ml. saline given over a period of 29 to 64 minutes. Adrenergic blockade was found to reduce the increased venous pressure in congestive heart failure whereas it did not affect the venous pressure of normal subjects. A similar effect upon right auricular pressure was recorded in three normal persons who showed signs of marked anxiety and in this respect they differed from all other subjects who were fully relaxed. The reduction in venous pressure and right auricular pressure occurred irrespective of any changes in the cardiac output or alterations on the arterial side of the vascular system. The degree of reduction in right auricular pressure was directly proportional to the degree of its original elevation. The authors conclude that the elevation of venous and auricular pressure in congestive heart failure is in large part of nervous (adrenergic) origin. The observations also disclosed a reduction in peripheral vascular resistance as a result of adrenergic blockade which was not secondary to any change in cardiac competency. The fall in peripheral vascular resistance was greatest in those patients in whom it was originally highest. There was a transient increase in cardiac output which was secondary to the change in peripheral vascular resistance. However, there was no correlation between the fall in right auricular pressure and the transient increase in cardiac output. There was evidence that Dibenamine did not increase the cardiac output by blocking adrenergic impulses to the heart. The increase in cardiac output was associated, in all subjects with heart disease, with a fall in the arterio-venous oxygen difference and in the utilization of oxygen. However, there was no consistent improvement in vital capacity or the Harrison's index.

The authors conclude that when the heart starts to fail, there is no gradual passive decline of the efficiency of the circulation, instead the whole vascular system is rebuilt by reflexes originating probably in interoreceptors of the entire vascular bed stimulated either by a decline in pressure or by some metabolic changes, so far undefined.

ROSENBAUM

Loogen, F. and Böhm, W.: Isolated Amyloidosis of the Heart. Ztschr. f. Kreislaufforsch. **43:** 224 (Apr.), 1954.

A case is reported of a 62 year old man who died in untreatable congestive heart failure and at necropsy revealed isolated amyloidosis of the myocardium. The lesion involved both ventricles and atria but the endocardium and the valves were free. In no other organ was evidence found of amyloid degeneration.

The clinical symptomatology of this condition is discussed and the difficulties in differential diagnosis are pointed out. The following combination should suggest during lifetime the possibility of amyloidosis of the heart: severe heart failure resistant to therapy, a flabby heart with weak contraction at fluoroscopy, and P-R prolongation, low voltage and ST-T abnormalities in the electrocardiogram. From the pathogenetic point of view the reported case is classified as a rare instance of atypical isolated amyloidosis of the heart.

PICK

Orie, N. G. M., van Buchem, F. S. P. and Homan, N. P. A. A.: Heart Failure in Chronic Pulmonary Disease. Acta med. Scandinav. **148:** 123 (Fasc. 2), 1954.

The various factors in the development of congestive failure in chronic pulmonary disease a

eviewed in reference to pneumonectomy, M. Besnier Boeck disease, pure pulmonic stenosis, uncomplicated emphysema and emphysema complicated by infection. These observers confirm the opinion of earlier workers that the major factors are those of disturbances in gas exchange occurring in emphysema, particularly the low arterial blood oxygen saturation followed by increased cardiac output, overburdening of the heart by resultant hypercolemia and polycythemia, the influence of anoxia on the heart muscle, and the pulmonary vascular constriction. The influence of mechanical factors alone appeared small. Heart failure appeared to be triggered by bronchial infection producing a fall in arterial oxygen saturation to below 80 per cent. There may also be a toxic effect of infection upon the myocardium in some cases. Where there is myocardial disease due to coronary sclerosis, the condition of the myocardium is another factor in the development of cor pulmonale.

It is evident that intensive treatment of infection of the airways is of outstanding importance in the treatment of cor pulmonale. Oxygen therapy is also very important although oxygen should not be used in concentrations sufficient to depress ventilation. In addition to the other usual measures of treatment, phlebotomy is urged if there is an increase in total blood volume.

ROSENBAUM

Storstein, O. and Tveten, H.: Anomalous Drainage of Pulmonary Veins from the Right Lung to the Superior Vena Cava with Patent Foramen Ovale, as the Cause of Congestive Heart Failure in a 68-year-old Man. Acta med. Scandinav. **148:** 77 (Fasc. 2), 1954.

A man is described who was admitted to the hospital at the age of 68 years with congestive heart failure. The physical findings which included a snapping apical first heart sound, a gr. II-III systolic murmur, a short rumbling diastolic murmur, an accentuated pulmonic second sound and auricular fibrillation were suggestive of mitral stenosis. However, cardiac catheterization demonstrated anomalous drainage of two pulmonary veins into the superior vena cava. The left to right shunt amounted to 38 per cent of the pulmonary artery flow. The demonstration of a greater reduction of the oxygen saturation in the arterial blood than in the pulmonary venous blood was felt to be due to a persistent foramen ovale with a right to left shunt of 24 per cent of the systemic blood flow from the right to the left auricle. The pulmonary resistance was increased three times above the normal level, imposing a greater load upon the right ventricle, increasing its work to about three times normal and ultimately leading to right ventricular failure. It is stated that only three patients with this condition and a greater longevity have been reported.

ROSENBAUM

Fisher, J. W. and Dolehide, R. A.: Fatal Cardiac Failure in Persons with Thoracic Deformities. Arch. Int. Med. **93:** 687 (May), 1954.

The deformity in these people so hindered their general development that their appearance suggested dwarfism. The cardinal symptom is dyspnea which occurs after the deformity reaches its maximum, usually at the age of 18 to 20 years. Mild dyspnea is usually present for several years; however, the length of time from the onset of the more acute manifestations to death is relatively short, often only several months and occasionally only a few days. The mechanics of respiration are inefficient in kyphoscoliosis. In order to compensate for this inefficient mechanism, these people increase their respiratory volume. They overbreathe and therefore suffer the chief symptom—habitual dyspnea. The transition from simple dyspnea to severe symptoms marks the onset of pulmonocardiac failure. Many develop tachycardia, although the exact mechanism for this is unknown. Pulmonary infection, respiratory depressants, or any process that further reduces pulmonary function and vital capacity in the hunchback may lead to pulmonocardiac failure. Partial collapse and infection are but natural results in these poorly aerated lungs. Pneumonia, emphysema, bronchitis, bronchiectasis, and atelectasis are frequently associated, and pneumonic areas often fail to resolve in the usual manner. The mildest bronchitis may prove fatal to this type of patient, leading to asphyxia and death.

It is believed that deformity of the chest is frequently not appreciated as an etiologic factor in some cases of cardiac failure. Pulmonocardiac failure is not analogous to the usual cor pulmonale and would appear to stand alone in its clinical manifestations. Because murmurs simulating rheumatic heart disease and gallop rhythm are frequently present, these cases are often misdiagnosed and the chest deformity overlooked as the prime cause of the heart failure. It is hoped that with the increased use of cardiac catheterization, pressure changes in the various heart chambers may shed new light on the mechanism of this interesting condition.

BERSTEIN

CORONARY ARTERY DISEASE

Wilson, J. L. and Ward, J. H. Jr.: Acute Myocardial Infarction Treated by the Chair Rest Regimen. J. A. M. A. **155:** 226 (May 15), 1954.

Thirty consecutive patients with proved myocardial infarction have been treated by the chair rest regimen. Among the advantages noted with this method of treatment are: (1) lower mortality, (2) minimal incidence of complications, (3) improved patient morale, and (4) shorter convalescence with more rapid rehabilitation and return to gainful work. None of the complications occurring during treatment of the 30 patients, nor any of the 3 fatalities, were attributable to chair rest care. Ob-

servations in this series agree with findings of others that persons with acute coronary occlusion who are allowed to sit up in a chair receive more complete mental and physical rest resulting in fewer complications and a lower mortality rate.

KITCHELL

Lary, B. G. and deTakats, G.: Peripheral Arterial Embolism After Myocardial Infarction. J. A. M. A. **154:** 10 (May 1), 1954.

The authors report on 8 cases of peripheral systemic arterial embolism of the lower extremities after acute myocardial infarction in patients with no evidence of rheumatic fever. The time of onset of these emboli was correlated with the ambulatory status of the patients. From such observations attention was drawn to the possible factor of immediate or early ambulation in the production of embolic phenomena after myocardial infarction. None of these cases were treated with anticoagulants. Six died and there were 2 recoveries among these 8 patients who were not put to bed after coronary occlusion or whose bedrest was very short.

KITCHELL

Woldow, A., Chapman, J. E. and Evans, J. M.: Fat Tolerance in Subjects with Atherosclerosis: Heparin Effects upon Lipemia, Lipoproteins, and Gamma Globulin. Am. Heart J. **47:** 568 (Apr.), 1954.

The occurrence of an increased degree and duration of alimentary lipemia is confirmed in subjects with coronary artery disease in comparison with normal subjects. At three hours after a fat meal, precipitable lipoproteins and lipemia are higher in subjects with coronary artery disease than in normal subjects. At five hours after fat loading, the levels of lipemia and lipoprotein are returning toward fasting in normal subjects while remaining elevated in subjects with coronary artery disease. It appears that heparin or a heparin-like substance may be an active factor in normal subjects and initiates the response in subjects with coronary artery disease. The reduction in gamma globulin concentration by heparin both *in vivo* and *in vitro* suggests that a heparin-globulin reaction may occur in association with clearing of lipemia.

RINZLER

Geever, E. F.: Fatal Coronary Heart Disease. A.M.A. Arch. Int. Med. **93:** 658 (May), 1954.

Clinicopathologic analysis is presented of 100 consecutive and unselected cases of fatal coronary heart disease with complete necropsy examinations. Although some overlapping occurs, at least six clinicopathologic patterns are identified and classified according to the predominant feature. They are: (1) orthodox-occlusion with or without infarction; (2) myocardial infarction without occlusion; (3) subacute or chronic congestive failure; (4) abrupt death, no new occlusion or new infarction found; (5) clinical features of fresh infarction, none found; and (6) death characterized by cerebral embolic or thrombotic episodes.

Other features, such as aneurysm formation, rupture, character of the occlusion time required for myocardial infarction, survival time, and precipitating factors in abrupt death, are presented and discussed.

BERNSTEIN

Haubrich, R. and Odenthal, H.: Myocardial Infarction in the Kymogram and Electrokymogram. Cardiologia **24:** 225 (Fasc. 4), 1954.

In patients with myocardial infarction, the electrokymogram is superior to the ordinary kymogram in the detection and accurate analysis of abnormal pulsations. This is demonstrated on 6 patients, 2 weeks to 2 years after myocardial infarction was established with certainty on clinical or electrocardiographic grounds. A silent portion of the cardiac border, supposedly a cardinal feature of myocardial infarction in the kymogram, is often absent, and if found, nearly always can be identified as an artefact. Instead, a paradoxical systolic outward movement of a circumscribed area has to be considered as the pathognomonic sign, but this is clearly demonstrable only in the electrokymogram. It occurs within few weeks after the infarction, is not related to an aneurysmatic prominence of the ventricular wall, and remains a significant sign even in patients with old infarcts, without any electrocardiographic abnormalities, or those with atypical clinical features.

PICK

Kroop, J. G. and Shackman, N. H.: Level of C-Reactive Protein as a Measure of Acute Myocardial Infarction. Proc. Soc. Exper. Biol. & Med. **86:** 95 (May), 1954.

An alpha globulin, which appears in serum when inflammation is present in the body, forms a precipitate with the somatic-C polysaccharides of the pneumococcus and is called C-reactive protein. Numerous studies have shown its existence when any type of inflammation is present. This precipitin test was thought to be useful in determining "inflammation" associated with myocardial infarction. In seven patients with coronary occlusion and signs of myocardial infarction, sera examined gave positive precipitin tests for C-reactive protein. In six patients with signs of coronary insufficiency, but without signs of myocardial infarction, the sera examined failed to show positive precipitin tests for this protein. It is concluded from these few observations that this test is a good indicator of myocardial necrosis and "inflammation."

HARVEY

Krook, H.: Acute Non-specific Pericarditis. Study in 24 Cases Including Descriptions of 2 with Later

Development into Constrictive Pericarditis. Acta med. Scandinav. **148:** 201 (Fasc. 3), 1954.

The material presented is drawn from a review of the records of all cases of pericarditis and all cases of acute myocardial infarction in patients under age 45 years studied in the Malmo Hospital over a period of 10 years. There were 21 cases of acute nonspecific pericarditis, by far the most common type of acute pericarditis. The various characteristics of this disorder are reviewed with particular emphasis upon comparison with the manifestations of myocardial infarction. The observations reported here correspond closely with those of previous reports. It is emphasized that the pain in this type of pericarditis is accentuated by deep respiration, cough and motion and that this occurs early after the onset of the disease, whereas such correlation appears late when associated with myocardial infarction. Possible occurrence of peritoneal serositis as a manifestation of generalized serositis is mentioned.

Two cases are described in which the onset of acute, apparently non-specific pericarditis was followed by the development of a picture of chronic, constrictive pericarditis. One patient was operated upon 6 months and the other 20 months later. The results of surgical therapy were very satisfactory. Pathological study of the material removed showed no evidence of specific inflammation in the pericardium. In one of these two cases the onset was less acute than usual, there was no pain and only relatively slight elevation of the temperature. It is stated that the development of constrictive pericarditis following acute non-specific pericarditis has not been reported previously. The question is raised that some instances of chronic, constrictive pericarditis which are encountered and for which no clear cause can be demonstrated may have a background of unrecognized acute non-specific pericarditis.

ROSENBAUM

Hutton, J. F. K.: Calcification in the Left Auricle. Brit. J. Radiol. **27:** 306 (May), 1954.

The author reports two cases of calcification in the left auricle. In one, the calcification took the form of an almost complete ring 8 cms. in diameter while the other probably involved the auricular appendage. There was no difficulty in differentiating these calcifications from calcification of a mural thrombus, of a calcified valve, or calcification of the valvular annulus.

SCHWEDEL

Galbraith, B. T. and Norman, S. L.: Dissecting Aneurysm of the Aorta. A Diagnostic Approach. New England J. Med. **250:** 670 (Apr. 22), 1954.

This report is concerned with a review of the literature and nine cases of dissecting aneurysm of the aorta observed by the authors. The diagnosis was made during life in five of the nine cases. It is of interest that three of the cases were seen in a single year in a town of 20,000 population. It is pointed out that the diagnosis will rarely be missed if it is considered in every catastrophic condition which begins abruptly and is not quite readily diagnosed as something else. Bedside observation for murmurs, changes in pulsations and other signs and symptoms are said to be more valuable in diagnosis of this condition than laboratory studies. Hemoptysis occurred in three of the nine cases reported here and is said to be slight and easily overlooked in some instances. The presence of a pale, moist, cold drawn facies of shock together with a persistently elevated blood pressure is said to be quite characteristic of this disorder. Hyperbilirubinemia was present in one-third of the cases observed by this author and it is suggested that this is due to dissection of or pressure upon the arteries of the celiac axis and mesentery.

ROSENBAUM

Danish, J. M.: Mediastinal Emphysema Complicating Myocardial Infarction. New England J. Med. **250:** 677 (April 22), 1954.

The case of a man 78 years of age is reported. The patient had an acute myocardial infarction after having had angina pectoris for 10 years. One week after the infarction occurred he developed acute pulmonary edema associated with severe dyspnea. Thereafter he developed mediastinal emphysema which was attributed to the cough accompanying the acute heart failure. Attention was directed to the mediastinum when subcutaneous emphysema was discovered. This is believed to be the first report of mediastinal emphysema complicating recovery from myocardial infarction.

ROSENBAUM

Guglielmo, L. and Guttadavro, M.: Anatomic Variation in the Coronary Arteries. An Arteriographic Study in Living Subjects. Acta Radiol. **41:** 393 (May), 1954.

The authors discuss in detail the anatomic variations in the coronary arteries based on an analysis of the literature, then deal with coronary arteries visualized in the course of thoracic aortographies and angiocardiographies in 399 patients. They present variations in number (single coronary, the usual two arising separately or from a common trunk, supernumerary); origin within or outside of the sinuses of Valsalva; increase or decrease in the branches arising from either the right or left coronary arteries, the left descending and circumflex branches, and preponderance of either the right or left arteries.

In 145 patients in whom contrast filling of the coronary arteries was obtained, both the right and left coronary arteries were invariably present. The variations most frequently encountered were those of the left coronary artery, either by increased number of left branches (three instead of the usual two), or by decrease because of the origin of the

circumflex and left descending by a single trunk. Variations in the anterior descending branch occurred rarely, but fairly frequently involved the circumflex branch.

The concept of preponderance of the left or right coronary arteries could be made. In the opinion of the authors, however, this was justified only when it was clearly evident that the preponderant artery gave rise to one or more important ramifications which normally arise from the other coronary artery, and in this way supply a more extensive area than normally.

SCHWEDEL

Pojer, J. and Ninger, E.: On Atypical Cases of the Shoulder-Hand Syndrome Following Myocardial Infarction. Cardiologia **24:** 214 (Fasc. 4), 1954.

Among 95 cases with myocardial infarction, 15 complained of atypically localized persistent painful sensations and weakness and discomfort. The patients showed trophic alterations in the upper extremities. In some of the cases, these symptoms preceded the myocardial infarct. The authors feel that such cases represent abortive forms, or equivalents, of a shoulder hand syndrome.

PICK

ELECTROCARDIOGRAPHY

Shaw, C. McK., Jr., Goldman, A., Kennamer, R., Kimura, N., Lindgren, I., Maxwell, M. H. and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity. VII. The Origin of the Coronary QR Wave. Am. J. Med. **16:** 490 (Apr.), 1954.

Studying the circumstances under which coronary QR waves occurred in a series of 68 infarcts produced in dogs by coronary artery ligation, the authors found that a mixture of live and dead muscle in the outer ventricular layers was usually associated with the presence of coronary QR waves. Twenty-six QR waves recorded in direct surface leads from 23 infarcts were analyzed. The occurrence of coronary QR waves was independent of the status of the deeper ventricular layers. Patients with subendocardial infarcts were found to show precordial QR waves in some instances and normal R or Rs waves in other instances. In explanation the authors suggest that although pure subendocardial infarcts do not alter the QRS complex in precordial electrocardiograms, ventricles containing subendocardial lesions with some involvement of the superficial layers may yield precordial QR waves.

An explanation of the various types of QRS changes seen clinically after coronary artery occlusion is presented. Death of muscle in the outer ventricular layers eliminates or reduces the magnitude of the positive epicardial potential (R wave). Negative potentials (Q or S waves) transmitted through the dead subepicardial muscle further alter the depolarization complex. A mixture of live and dead muscle in the outer ventricular layers may thus result in a variety of QRS changes. The type of complex that occurs depends upon the relative magnitude and timing of the reduced positive epicardial potential and the transmitted potential.

HARRIS

Von Ahn, B.: The Electrocardiogram in Tobacco Smoking during Hypoxia. A Preliminary Account. Acta med. Scandinav. **148:** 101 (Fasc. 2), 1954.

The effect of tobacco smoking during hypoxia upon the electrocardiogram was studied in 46 normal males, two-thirds of whom were smokers. When hypoxia had been present for six minutes with stabilization of oxygen saturation, heart rate and respiratory rate, tobacco smoke from a cigarette or a cigar was introduced through a special lateral mouthpiece or nicotine was given by injection. A linear correlation was demonstrated between the height of the T waves and the simultaneously occurring increase in the heart rate. It was found that depression in the height of the T waves was no greater than would correspond to a similar increase in heart rate under physiological conditions. Except in isolated cases, hypoxia did not accentuate the effect of tobacco upon the electrocardiogram. The effect of nicotine was entirely or partly eliminated by means of dehydroergotamine. In the younger age group the non-smokers reacted more to prolonged hypoxia than did the smokers, possibly because the daily inhalation of small quantities of carbon monoxide in tobacco smoke had accustomed the latter to a small though slight degree of hypoxia.

ROSENBAUM

Southern, E. M.: Electrocardiography and Phonocardiography of the Foetal Heart. J. Obst. & Gynaec. Brit Emp. **61:** 231 (Apr.), 1954.

The history of foetal electrocardiography is reviewed. The instruments which the author adapted were a portable electrocardiograph used with a single stage resistance-coupled valve pre-amplifier employing photographic recording and a crystal microphone, amplifier and filter control of wide frequency with a second galvanometer fitted to the electrocardiograph. Recordings are made from electrodes of suction cup variety positioned over the abdomen giving wide angled diagonal leads from upper to lower quadrants over the gravid uterus. Interference factors are many, among which are thickness of material abdominal wall, amount of amniotic fluid, foetal and uterine movement, and material bowel movement. Recordings were made on 190 pregnant women and showed 85.8 per cent positive tracings. The clinical applications are to establish viability, multiple pregnancy, and evaluation of foetal distress. Good illustrations of sample records are presented.

HARVEY

Berliner, K. and Huppert, V. F.: Benign Ventricular Premature Systoles. Cardiologia **24:** 184 (Fasc. 3), 1954.

The electrocardiographic appearance of ventricular premature systoles was compared in 58 patients clinically free from heart disease and in 54 patients with various types of cardiac pathology. Particular attention was paid to the QRS deviation of the premature beats. In the normal group it varied between 0.064 and 0.16 second, the last figure occurring only in one case. In the abnormal group, QRS varied widely between 0.08 and 0.20 second. The authors believe that a QRS of 0.16 second may be considered as the dividing line between "benign and pathologic" ventricular premature systoles. The finding of premature beats with QRS longer than 0.16 second should arouse the suspicion of heart disease.

PICK

Elster, K. and Luterotti, M.: Right Ventricular Hypertrophy in the Electrocardiogram and the Proportion of Mass of the Two Heart Chambers. Ztschr. f. Kreislaufforsch. **43:** 244 (Apr.), 1954.

In 17 specimens of hearts with varying degrees of right ventricular hypertrophy the muscle mass of the two ventricles was determined by a modified method of W. Mueller and correlated with electrocardiographic findings. On the basis of these investigations and of previous data in the literature the authors arrived at the following conclusions.

Signs of right ventricular hypertrophy occur in the electrocardiogram only when the mass of the right ventricle equals or exceeds that of the left ventricle. Two types of electrocardiographic alterations can be distinguished. The first, or infantile type, is characterized by the absence of conduction delay in contrast to the second, or adult type, which, in addition to signs of ventricular hypertrophy, shows evidence of late activation of the right ventricle. Conduction disturbances per se have no relationship to the mass of the right ventricular muscle and merely indicate its damage by chronic strain. The underlying conduction disturbance may be located at the synapses or specific with ordinary muscle fibres. A conduction disturbance, when developing parallel to signs of hypertrophy may mask the latter. Therefore an intraventricular block may be used as indirect evidence of ventricular hypertrophy.

Inverted T waves in the right precordial leads are not due to "muscular damage" but merely the expression of a changed spatial position of the T vector, secondary to the altered mass relationship of the two ventricles.

PICK

Flothschuh, K. and Zemke, D.: Investigations Concerning the Usefulness of Einthoven's Triangle in a "Truncus Model". Comparison of Measured Values with Data Calculated by Einthoven's and Gillard's Formulas. Ztschr. f. Kreislaufforsch. **43:** 321 (May), 1954.

In a plexiglass model of the human trunk an electrical field was created by introduction of electrical dipoles of known magnitude and direction. Einthoven leads were recorded from the surface of the model and the correctness of vectors calculated from such leads was tested against the properties of the actual vector. As long as the source of the potential was kept in the center of the model the correlation was good. When it was moved to an eccentric position corresponding to the location of the heart, considerable differences were found whether Einthoven's or Gillard's formulas were used for the calculations. When however, several dipoles of different direction were used with each perpendicular to "heart borders" the differences cancelled out and the estimated potential differences came very close to those actually present. On the basis of such model experiments it appears that determinations of the electrical axes from Einthoven leads as commonly used in human electrocardiography are valid because of subtraction of possible sources of error related to the eccentricity of the various dipoles of the heart.

PICK

Kennamer, R. and Prinzmetal, M.: Depolarization of the Ventricle with Bundle Branch Block. Studies on the Mechanism of Ventricular Activity. X. Am. Heart J. **47:** 769 (May), 1954.

Intramural and intracavity potentials in experimental left and right bundle branch block were recorded by means of specially designed plunge electrodes.

Purely or primarily positive depolarization complexes were registered from all parts of the cavity in ventricles with complete bundle branch block. In incomplete block, the cavity yielded a variety of complexes ranging from QS waves of diminished amplitude to Rs waves. All parts of the wall of the ventricle with complete bundle branch block yielded predominantly positive depolarization complexes. Intraseptal, intracavity, intramural and epicardial leads from ventricles with bundle branch block were compared with respect to timing and magnitude of the depolarization complexes. The results were inconsistent with the classic theory that the initial portion of the R wave in epicardial and precordial leads results from transmission of septal potentials through the cavity and ventricular wall.

The large positive complexes recorded over ventricles with bundle branch block appear to result entirely from depolarization of the underlying wall. These complexes are abnormal in amplitude, width and shape because depolarization of the wall occurs in a markedly abnormal manner.

MAXWELL

Smith, L. A., Kennamer, R. and Prinzmetal, M.: Studies on the Mechanism of Ventricular Ac-

tivity IV. Ventricular Excitation in Segmental and Diffuse Types of Experimental Bundle-Branch Block. Circulation Research **2**: 221 (May), 1954.

The pattern of ventricular excitation before and after bundle-branch block was studied in 20 dogs by means of multiple unipolar direct leads. In complete bundle-branch block in addition to a delay in the onset of activation of the blocked ventricle, the spread of activation, once begun, occupies a greater time interval; thus, free wall as well as septal factors contribute to the increased intraventricular conduction time.

Two types of incomplete bundle-branch block are reported. In the segmental type, delayed excitation was found in only a portion of the homolateral ventricle, with relatively slight alterations of the limb leads. In the diffuse type, various degrees of delayed excitation were demonstrable in all areas of the homolateral ventricle; this type was accompanied by moderate changes in the limb lead complexes.

The findings suggested that certain segments of the ventricular myocardium are supplied by fixed portions of the conducting system, without cross connections operating physiologically. The clinical implications of these studies were considered briefly.

MAXWELL

ENDOCRINE EFFECTS ON CIRCULATION

Pullman, T. N. and McClure, W. W.: The Relative Roles of Sodium and Chloride in the Salt-Retaining Action of Desoxycorticosterone in Man. Metabolism **3**: 240 (May), 1954.

Normal young males received 40 mg. of DCA while receiving varying intakes of sodium and chlorides. When the intake was low in sodium and high in chloride there was no diminution of salt excretion. When the intake was high in sodium and low in chloride there was a marked diminution of salt excretion. Either a low sodium intake or a low sodium was responsible for the abolition of the salt-retaining effect of DCA. This modification of DCA action could not be attributed to reduction of chloride intake or output. It appears that either a low sodium intake reduces the renal tubular response to DCA or that tubular retention of sodium is quantitatively limited so that, when excretion is at a minimum, DCA cannot decrease it further.

SHUMAN

Russek, H. I., Zohman, B. L. and Russek, A. S.: Risk of Thromboembolic Complications from Cortisone Therapy. Am. Heart J. **47**: 653 (May), 1954.

The administration of cortisone and corticotropin (ACTH) has been reported by some authors to cause an increased coagulability of the blood, particularly when preexisting serious vascular disease or thrombophelic tendencies are present. For this reason, the authors reported their experience with 86 consecutive patients with serious vascular disease who received a course of cortisone in relatively large dosage.

The patients had diagnoses of angina pectoris, coronary insufficiency, acute myocardial infarction, cerebrovascular occlusion (hemiplegia), apoplectic stroke and congestive heart failure; they all received large dosages of cortisone in a course of therapy generally extending over a period of three weeks. In these patients no thromboembolic phenomena or other vascular complications were encountered during the administration of the drug or following its withdrawal. No specific measures were taken to prevent thromboses except for encouragement of active and passive motion and frequent change of position in bed.

The authors conclude that the theoretic danger of thrombotic complications from the use of cortisone is not clinically significant and that underlying disease of the heart or blood vessels need not preclude such therapy when proper supervision and simple precautions are instituted.

MAXWELL

Rosenman, R. H., Freed, S. C. and Smith, M. K.: Effect of Cortisone on Blood Pressure of Hypertensive Rats Deprived of Dietary Potassium. Am. J. Physiol. **177**: 325 (May), 1954.

Unilateral nephrectomized rats were rendered hypertensive by renal figure-of-eight ligature or desoxycorticosterone. Their blood pressure was then lowered by dietary potassium restriction. Cortisone acetate restored the elevation in blood pressure even though the potassium deficit persisted.

OPPENHEIMER

Roehm, D. C.: Trichinosis: Report of Case Manifesting Myocarditis, Encephalitis and Radial Neuritis; Response to ACTH; Review of Literature Regarding the Erythrocyte Sedimentation Rate. Ann. Int. Med. **40**: 1026 (May), 1954.

A 34 year old bachelor carpenter was admitted in a state of amnesia. Three weeks prior to admission the patient developed nausea and vomiting, followed in several days by watery diarrhea. The second week of illness, burning of the eyes became quite severe, and a physician administered penicillin for "conjunctivitis." Swelling then developed about the eyes as well as the hands and feet. Vomiting had ceased by this time, but diarrhea remained intractable. Finally, several days before admission, the patient had evidenced extreme weakness and loss of memory. Physical examination on admission revealed the following: the temperature was 101 F., the pulse was 110, respirations were 16 and the blood pressure was 95/96 mm. of Hg. The patient was an acutely ill, dazed white male who gripped the examining table with both hands in order to sit upright. He was unable to state his age or home address, or to recount the events of the preceding three weeks of his illness. At times he laughed weakly

when he could not reply satisfactorily but he made no effort to confabulate. There was no outspoken periorbital edema. The heart sounds were distant; no murmurs were present. Aside from the sensorial defect, neurologic examination was not remarkable. The clinical diagnosis of trichinosis was established on the day after admission by muscle biopsy. Electrocardiographic abnormalities reached their peak seven weeks after the onset of illness. ST and T wave abnormalities persisted at least until the eleventh week but six months later all findings were within normal limits at rest and after exercise.

The striking finding in this case was the rapid termination of three crises by ACTH. It was also evident that this therapy did not prevent permanent injury to the brain and very likely to the heart as well.

WENDKOS

HYPERTENSION

Taylor, R. D., Corcoran, A. C., Dustan, H. P. and Page, I. H.: Further Evaluation of Hydralazine In Treatment of Hypertensive Disease. Arch. Int. Med. **93:** 705 (May), 1954.

A reappraisal of a group of patients treated with hydralazine confirms the fact that about half the patients respond favorably to the drug and shows that the response may persist for as long as 30 months. A favorable response is reflected not only in reduction of diastolic pressure to levels averaging less than 110 mm. Hg, but also in improved renal, cerebrovascular and cardiac status and, most impressively, in decreased mortality, which among responders is about one-fifth of the rate among non-responders.

Discordant views on the effectiveness of hydralazine in the treatment of hypertensive disease seem attributable to various factors (1) a large proportion of patients do not respond; (2) impatience in the desire for a prompt depressor effect; (3) overestimation of the significance of side-effects; (4) the lack of an ordered schedule of treatment; and (5) last in order, but not in importance, reliance on casual office or outpatient blood pressure determinations in evaluating response. A regime therapy is outlined by which dosage is slowly increased to 800 mg. daily or to any lower fully effective dose, and slowly reduced thereafter to the minimum dose which will maintain the hypotensive effect.

BERNSTEIN

Fischin, A. M., Semerars, D. and Robertazzi, R. W.: The Control and Management of Hypertensive Crises Developing During Surgical Procedures. Anesthesiology **15:** 262 (May), 1954.

The authors discuss the occurrence of hypertensive crises of reflex origin as seen by the anesthesiologist during surgical procedures. In patients with transection of the spinal cord at or above the fifth thoracic segment, hypertensive states resulting from the mass autonomic reflex response to surgical stimulation could be abolished or prevented by the intravenous administration of hexamethonium. Similar results were obtained with this drug in patients with expanding intracranial lesions and Graves disease. Case records demonstrating the controllability and the clinical applications of the method are presented.

SAGALL

Ciliberti, B. J., Goldfein, J. and Rovenstine, E. A.: Hypertension During Anesthesia in Patients with Spinal Cord Injuries. Anesthesiology **15:** 273 (May), 1954.

The occurrence of hypertension in paraplegic patients subjected to anesthesia and surgical procedures was studied. In twenty-seven patients with complete lesions at the level of the fifth thoracic segment or above significant elevations of blood pressure (a systolic rise of 50 mm. of mercury or more) was observed in 42.5 per cent of the fifty-four times that they had undergone surgical manipulation and general anesthesia. Hypertension did not occur consistently in the same patients but appeared to be related in some way to the strength of the stimulus applied. The reflex could be controlled with autonomic ganglion blocking agents such as hexamethonium or tetraethylammonium chloride. A second group of thirty-five patients with complete lesions at the sixth thoracic segment or below underwent general anesthesia fifty-one times. Only two of these patients showed a marked rise in systolic pressure. In thirteen patients in the first group spinal anesthesia had been employed and no instance of hypertension or headache due to reflex activity was observed. The ideal method of the treatment of such hypertensive reactions would be the removal of the stimulus. In most cases, however, this is not possible since the trigger mechanism is not readily apparent. The reflex can be controlled by autonomic ganglion blocking drugs or the utilization of spinal anesthesia for surgical procedures on the lower part of the abdomen or the extremities in these patients.

SAGALL

Daniel, P. M., Prichard, M. L. and Ward-McQuaid, J. N.: Total Nephrectomy in Rabbits with Chronic Hypertension. Clin. Sc. **13:** 211 (May), 1954.

The authors repeated experiments like those previously reported, in which the sole remaining ischemic kidney of hypertensive rabbits was removed several months after the application of a clip to the renal artery. In all eight rabbits the hypertension was maintained even after the sole remaining kidney was removed, and the blood pressure fell only when the rabbits were terminal. Histological examination showed no vascular lesion.

The evidence appears to favor the theory that an extrarenal factor is responsible for maintaining the raised blood pressure in experimental hypertension

of long standing. It also appears that the uremia which develops in hypertensive rabbits after total nephrectomy does not cause fibrinoid necrosis in the few days of survival following the nephrectomy.

ENSELBERG

Pickering, G. W., Fraser Roberts, J. A. and Sowry, G. S. C.: The Etiology of Essential Hypertension. III. The Effect of Correcting for Arm Circumference on the Growth Rate of Arterial Pressure with Age. Clin. Sc. **13:** 267 (May), 1954.

The authors previously showed that the average arterial pressure rose with age in the general population. In order to evaluate the influence of the circumference of the arm on the data, it was decided to make observations on a second population sample, consisting of 209 subjects. The second population sample was very similar to the first. In general there was not much change in arm circumference with age. Women's arms tended to become fatter and men's arms thinner, but the tendency was slight. When systolic and diastolic pressures were corrected for arm circumference by using previously reported data, the growth rate of arterial pressure with age was not significantly changed.

ENSELBERG

Hamilton, M., Pickering, G. W., Fraser Roberts, J. A. and Sowry, G. S. C.: The Etiology of Essential Hypertension. IV. The Role of Inheritance. Clin. Sc. **13:** 273 (May), 1954.

The authors briefly review previous studies of inheritance in hypertension. Their own study is based upon 2000 subjects and upon the first degree relatives of those with as well as without hypertension. The relatives of subjects with essential hypertension showed higher pressures at all age groups than the general population. There was a general parallelism of the intensity of hypertension in the subjects and their relatives. This was more striking in the higher ranges of pressure. The authors feel that they have demonstrated two factors in the pathogenesis of hypertension, age and inheritance. It is possible that a third factor, environmental influences, may be at least as important.

ENSELBERG

von Euler, U. S., Hellner, S. and Purkhold, A.: Excretion of Noradrenaline in Urine in Hypertension. Scandinavian J. Clin. & Lab. Investigation **6:** 54 (Fasc. 1), 1954.

The noradrenaline secretion in the urine was measured by the technique of Euler and Hellner in 500 unselected cases of essential hypertension. The noradrenaline secretion was within normal limits in 66.2 per cent (less than 57.6 μg per 24 hours) and increased in 16.4 per cent of the cases (above 86.4 μg per 24 hours). The proportion of males with high excretion levels was in excess up to age 30 but not in the age groups beyond that level. It is mentioned that the percentage of hypersecretors corresponds closely to the percentage of patients showing a favorable response in blood pressure after sympathectomy and that although this may be fortuitous, it is suggestive of a causal relationship. The occurrence of an increased noradrenaline excretion and presumably production, in essential hypertensives suggests that this factor may be of significance in the pathogenesis in a certain proportion of such cases.

ROSENBAUM

Silver, A. W., Kirklin, J. W., Ellis, H. F. Jr. and Wood, E. H.: Regression of Pulmonary Hypertension After Closure of Patent Ductus Arteriosus. Proc. Staff Meet., Mayo Clinic. **29:** 273 (May), 1954.

Evidence is presented indicating that the severe pulmonary hypertension sometimes associated with a patent ductus arteriosus may be reversible (at least in some cases) after surgical closure of the ductus. In the patient presented, when the ductus was closed, the factor of increased flow was eliminated. Anatomic changes in the pulmonary vessels, however, are not immediately reversible. Indeed, intimal lesions, which were not seen in this patient, are probably not reversible since they are mainly composed of fibrous tissue. Medial hypertrophy of the pulmonary arteries, being muscular in nature, should be reversible once the stimulus for this hypertrophy is removed. This is the objective of those who advocate early surgical attack on the ductus in those patients with pulmonary hypertension.

SIMON

Wyngaarden, J. B., Keitel, H. G. and Isselbacher, K.: Potassium Depletion and Alkalosis. Their Association with Hypertension and Renal Insufficiency. New England J. Med. **250:** 597 (Apr. 8), 1954.

This report is concerned with a man aged 46 years with malignant nephrosclerosis, a disorder commonly associated with excessive potassium loss in the urine and an inability to conserve fixed cations. This patient displayed evidence of uremia, alkalosis and potassuria with hypokalemia. On two occasions potassium and sodium chloride administration restored positive potassium balance, with increases in serum and erythrocyte concentrations of potassium, rise in serum chloride concentration and fall in serum carbon dioxide content to normal. When the potassium and sodium chloride supplements were omitted the potassium deficiency returned, the serum chloride and sodium concentration fell once more and the carbon dioxide content rose. In this case the alkalosis could not be attributed to gastrointestinal losses, adrenocortical hyperfunction, ingestion of alkali or use of mercurial diuretics. There were alkaline urines in this patient suggesting a shift of hydrogen into cells contributing to the extra-cellular alkalosis. If this alkalosis had been of renal origin,

a id urine would have been present. It is also pointed o t that the alkalosis may have caused further renal i pairment and loss of potassium.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Hennamer, R. and Prinzmetal, M.: The Cardiac Arrhythmias. New England J. Med. **250:** 509 (Mar. 25), **250:** 562 (Apr. 1), 1954.

Recently developed knowledge concerning the arrhythmias is reviewed at length in this pair of reports. Newly developed hypotheses are contrasted with those of earlier students of the problems.

Concerning the atrial arrhythmias, the circus-movement theory is contrasted with that of a repetitively discharging ectopic focus. Recent high-speed cinematographs in a patient undergoing mitral commissurotomy and having spontaneous auricular flutter are said to have shown simultaneous contraction of the left and right atrial appendages, evidence in accord with the ectopic focus theory. The study of the course of the atrial activation wave by means of esophageal and precordial leading is said to have disclosed some evidence in accord with and some in conflict with the circus-movement theory. Limb and precordial leads in a large number of cases of spontaneous flutter showed isoelectic intervals, evidence supporting the ectopic focus theory. Demonstration of P′ and Ta components in the undulatory waves of flutter and measurement of the P′–P′ intervals is also felt to support the ectopic focus hypothesis, as does the production of flutter by establishing an ectopic focus with aconitine in dogs by the technique of Scherf. The production of prolonged periods of poststimulatory flutter after the intercaval bridge was blocked with cocaine or crushed before electric stimulation by Rosenblueth and Garcia Ramos is said to be the strongest support for the circus-movement theory since the work of Lewis.

High-speed cinematographs of the exposed heart, direct lead electrocardiograms and double-lead electrocardiograms recorded with a cathode-ray oscilloscope are all reported to have yielded evidence suggesting a multifocal disturbance rather than a circus-movement mechanism in patients with auricular fibrillation. Spontaneous auricular fibrillation in man is said to be a chaotic heterorhythmic disturbance consisting of large waves at irregular rates of about 300 per minute and small waves appearing at much higher frequencies. Clinical fibrillation is considered to represent an advanced degree of conduction failure occurring when the atrial rate reaches a critical level, designated as the "fibrillation threshold." These authors state that there is no electrical or mechanical evidence of circus movement in direct-lead electrocardiograms or high-speed films recorded during surgery or in esophageal lead oscillograms in patients with auricular fibrillation.

Among the factors which have been observed to cause atrial arrhythmias are cardiac catheterization, emotional disturbances, digitalis, masked hyperthyroidism, and hemochromatosis. So far as disorders of rhythm associated with the Wolff-Parkinson-White syndrome are concerned, Fox and his associates are reported to have attributed them to a decrease in "vagus substance." Other investigators are reported to ascribe the Wolff-Parkinson-White syndrome to a disturbance of the atrioventricular node.

The authors have concluded that the commonly accepted criteria for the diagnosis of flutter are confusing and often meaningless. It is felt that there is no physiologic basis for distinguishing between atrial tachycardia with block and flutter. A proposal is reported whereby all arrhythmias now designated as atrial tachycardia or flutter would be classified as variants of supraventricular tachycardia with an added diagnostic term concerning the atrial rate, configuration of the atrial deflection and the site of the ectopic focus. It is mentioned that Wolff has pointed out that paroxysmal auricular fibrillation may be the earliest manifestation of pulmonary embolism.

Studies of ventricular extrasystoles and ventricular tachycardia have suggested that in this disorder contractions spread out radially in all directions from a single focus. Various types of study are said to have disclosed nothing to suggest a circus movement. Recent reports concerning the etiology of ventricular arrhythmias have included hypoxia, reflexes from vagal stimulation and anaesthesia—all during thoracic and general surgical procedures, cardiac catheterization, carotid sinus stimulation, eyeball pressure, tetraethylammonium chloride, Nikethamide, Dilatin, digitalis, quinidine, Pronestyl, potassium intoxication, emotional disturbances and exercise in patients with coronary insufficiency.

The drugs and measures employed in the treatment of disordered cardiac rhythm are also reviewed in detail. The authors favor the view that depression of excitability rather than depression of conductivity is responsible for the anti-arrhythmic action of quinidine. It is mentioned that acetyl strophanthidin is a very rapidly acting digitalis preparation but a few ominous toxic reactions have been reported and for this reason it is felt that oubain is considerably safer and its speed of action is sufficiently rapid. Although it was originally thought that Pronestyl was preferable to quinidine for intravenous therapy, this may not be true in the light of new developments regarding the administration of the latter drug. Furthermore, recent studies have not supported the initial belief that Pronestyl was far superior to quinidine in the treatment of ventricular arrhythmias.

ROSENBAUM

Litter, J. and Wood, J. E.: The Volume and Distribution of Blood in the Human Leg Measured *In Vivo*. I. The Effects of Graded External Pressure. J. Clin. Invest. **33:** 798 (May), 1954.

In the study of venous tone in the extremities, venous pressure-volume curves obtained by congestion of the venous tree may be useful. Such curves, however, should be measured from a constant reference point of venous volume and effective venous pressure. The authors describe a technic in which a constant base line is obtained when an external pressure equal to or greater than the natural local venous pressure is applied to the leg. This is done by measuring the volume of blood in the human leg by a plethysmograph at graded external pressures. In the course of these observations, it appeared that the combined volume of the capillaries, arterioles, and arteries is small regardless of the effect of pressures in these vessels. The volume and distribution of blood in the leg at rest are, essentially, functions of the effective venous pressure.

WAIFE

White, A. G.: Diabetes Insipidus Associated with Edema. Report of a Case with Discussion of the Physiologic Implications. New England J. Med. **250:** 633 (Apr. 15), 1954.

The author reports a case of diabetes insipidus in a man aged 58 years. The underlying lesion ultimately proved to be a primary bronchogenic carcinoma with metastatic destruction of the posterior lobe of the pituitary gland. In addition there was massive edema of the lower extremities believed to be due to sodium retention secondary to adrenocortical hyperfunction and congestive heart failure. Hypokalemia, hypernatremia and hyperchloremia were other features of the clinical picture. This patient is considered to be of particular interest from the point of view of water retention and edema formation in spite of the virtual absence of the neurohypophyseal antidiuretic hormone. It is concluded that this antidiuretic hormone may be a contributing factor in water retention in hepatic and cardiac disease but it is not, apparently, an absolutely essential one. It is also of interest that this patient developed pulmonary edema during a Hickey-Hare test (the intravenous administration of hypertonic saline solution) performed at a time when the rate of urinary flow exceeded the rate of the saline infusion.

ROSENBAUM

Felder, D., Russ, E., Montgomery, H. and Horwitz, O.: Relationship in the Toe of Skin Surface Temperature to Mean Blood Flow Measured with a Plethysmograph. Clin. Sc. **13:** 251 (May), 1954.

The authors describe a method of recording skin temperature and adjacent air temperature of the toes during venous pressure plethysmography. They showed that there was a fairly good relationship of blood flow to skin temperature at room temperature of 18.5 to 22.5 C. From the curve of correlation, several intermediary points can be ascertained: a constant skin temperature of 24 C. indicates a blood flow of 3 cc per 100 cc per minute; a temperature of 29 C., a flow of 10 cc; and a temperature of 32 C., a flow of over 30 cc per 100 cc per minute. The skin temperatures give a better indication of blood flow in the lower ranges. The air temperature within the cup averaged 3.3 C. higher than room temperature, but it was felt that this had no significant influence on flow.

ENSELBERG

Turner, L. W. and Lansbury, J.: Low Diastolic Pressure as a Clinical Feature of Rheumatoid Arthritis and Its Possible Etiologic Significance. Am. J. M. Sc. **227:** 503 (May), 1954.

An analysis of the hospital records of 320 patients with rheumatoid arthritis was made by the authors in order to compare admission blood pressures with the average pressure readings of an unselected group of patients from the literature. It was of interest to note that the average diastolic pressure in the arthritic group for all decades remained at the level of 75 mm. of mercury. The averages of diastolic pressures for control rises with each decade.

ABRAMSON

King, B. D., Elder, J. H., Proctor, D. F. and Dripps, R. D.: Reflex Circulatory Responses to Trachial Intubation Performed Under Topical Anesthesia. Anesthesiology **15:** 231 (May), 1954.

The circulatory changes produced in twenty-one fully conscious patients in regard to the blood pressure, cardiac rate and cardiac rhythm were studied after topical anesthesia, laryngoscopy and tracheal catheter insertion. In most cases the application of topical anesthesia was followed by an increase in blood pressure and pulse rate. Similar changes were also produced by laryngoscopy and tracheal intubation. The latter procedures, however, occasionally induced transient cardiac arrhythmias. These were not frequent or serious and consisted mainly of premature ventricular contractions. The responses observed after instrumentation were qualitatively similar to those seen during light general anesthesia. Although the importance of these reflex circulatory responses to intubation in the conscious and anesthetized patient cannot be completely assessed the authors believe that the pressor effect, increased pulse rate, and cardiac arrhythmias so induced probably would not be harmful to the normal circulatory system. The most logical attitude towards these circulatory reflexes is one of moderation, for procedures aimed at eliminating or preventing them may be more detrimental to the patient than the condition that the physician is trying to avoid.

SAGALL

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

AHA ANNOUNCES AWARDS TO 115 INVESTIGATORS

A total of 112 research investigatorships and fellowships have been approved by the Board of Directors of the American Heart Association for the fiscal year beginning July 1, 1955. Included were 3 career investigators, 48 established investigators and 64 research fellows. This is the first of two groups of awards to be announced by the National Office this year. Monies for these awards are provided by receipts from the 1954 Heart Fund.

The newest awards approved by the Board amount to $695,000, nearly 50% more than the $509,300 allocated for investigatorships and fellowships last year. An additional $489,756 was given in grants-in-aid last year. The latest allocations bring the total amount designated by the Association and its affiliates for research support to more than $10,000,000 since the reorganization of the Association as a voluntary health agency in 1948. The list of award winners follows at the end of this section.

NEW ASSOCIATION STATEMENT CONTAINS LATEST RHEUMATIC FEVER KNOWLEDGE

The revised Association statement on "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections," which was published in the February issue of *Circulation*, is now available in reprint form from the Association and its affiliates as well as from the National Heart Institute of the United States Public Health Service and state and local health departments. The statement incorporates knowledge of new advances in preventive technique made since the Association's first rheumatic fever prevention statement was published in January, 1953.

The statement is being distributed to more than 100,000 physicians by the Association and to 1,500 state and local health officers by the National Heart Institute. It is also being used as a basis for printed and audiovisual materials designed to give parents, teachers, nurses and social workers the knowledge needed to cooperate with the medical profession in preventing rheumatic fever. The medical prophylaxis statement deals with the two major aspects of rheumatic fever control, prevention of first attacks and prevention of recurrences. It was prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis appointed by the American Heart Association's Council on Rheumatic Fever and Congenital Heart Disease.

In order to secure the informed and intelligent cooperation from the general public which is necessary to the medical profession's success in the effort to prevent rheumatic fever, the American Heart Association and its affiliates in conjunction with the National Heart Institute are launching a vigorous campaign to guide communities toward the establishment of effective rheumatic fever prevention programs. A "Stop Rheumatic Fever" educational materials unit has been prepared to provide parents, teachers, nurses and social workers with information needed for such cooperation. The following materials are included:

1. "Now You Can Protect Your Child Against Rheumatic Fever," a pamphlet which features a chart advising parents on "When to Call Your Doctor and What to Tell Him About Your Child's Sore Throat."
2. A cartoon film, "Stop Rheumatic Fever," produced by Transfilms, Inc. for the National Heart Institute in cooperation with the American Heart Association, which presents to a lay audience basic information on rheumatic fever prevention through control of streptococcal infections.
3. A discussion guide for use with the film which makes it a suitable accompaniment for a physician's lecture on rheumatic fever.

4. A pamphlet for adults, "Stop Rheumatic Fever," summarizing the information contained in the film.
5. "What You Should Know About Rheumatic Fever," a question-and-answer leaflet for the general public which gives background information on rheumatic fever.

Reprints of the lay materials as well as of the prevention statement for physicians are available from local heart associations and health departments or from the American Heart Association, 44 East 23rd Street, New York 10, N. Y., and from the Heart Information Center, National Heart Institute, United States Public Health Service, Bethesda 14, Maryland.

PROTECTION AGAINST ENDOCARDITIS IN DENTAL MANIPULATIONS

The problem of protecting dental patients against bacterial endocarditis is treated extensively in the leaflet, *How the Dentist Can Protect His Patient Against Bacterial Endocarditis*. The illustrated folder urges dentists to ask patients undergoing extractions or any other dental procedures whether they have had or do have rheumatic heart disease or a congenital heart defect. When the answer is affirmative, prophylactic utilization of penicillin is recommended. The dosage and methods of administration are specified in a chart which is included in the leaflet. The folder was prepared by the Association in consultation with the American Dental Association.

CARDIAC CONVALESCENT HOMES

As active rheumatic fever abates, the physician is often confronted with the problem of deciding whether a child will do better during the convalescent state in his own home or in an institution. In this situation, the newly-issued manual, *Standards for General Convalescent Homes Caring for Cardiac Children*, provides a reference guide. The statement, originally prepared by the New York Heart Association, is now available through the American Heart Association and its affiliates.

CARE OF YOUNG RHEUMATIC PATIENT IS SUBJECT OF NEW FILM

The treatment and rehabilitation of a youngster after a rheumatic fever attack is dealt with in "The Valiant Heart" a half-hour human interest film produced for and being distributed by the Association and its affiliates.

"The Valiant Heart" particularly emphasizes the importance of mobilizing all community resources, starting with the young patient's immediate family and including the physician in general practice, the cardiologist, the town hospital, the public health nurse, the school authorities and the neighbors, in caring for the rheumatic fever victim through the acute and convalescent stages. The film was produced for the American Heart Association by MPO Productions with funds provided by E. R. Squibb and Sons. George C. Stoney was the writer and director.

DIAGNOSIS OF CONGENITAL HEART DEFECTS

A revised edition of the manual, *Diagnosis of Congenital Heart Defects in General Practice*, has been prepared for the Association and its affiliates by Regina Gluck, M.D., Assistant Clinical Professor of Pediatrics, Children's Medical Service, Bellevue Hospital, New York. The new edition contains expanded information on those defects which may be treated surgically—patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot, coarctation of the aorta and vascular ring. It emphasizes restraint on the part of a general practitioner in either predicting surgery or definitely ruling out the possibility until the subject has been fully examined by a cardiologist. It also cautions against imposing excessive restrictions on cardiac children.

Diagnosis of Congenital Cardiac Defects is available to cardiologists, general practitioners, hospitals and clinics from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

PLAN THREE DAYS OF SCIENTIFIC SESSIONS AT ANNUAL MEETING

The annual Scientific Sessions are planned

for the first three days of the 1955 American Heart Association Annual Meeting to be held at the Jung Hotel, New Orleans, October 22–27.

REGIONAL MEETINGS

A series of six regional meetings in which both medical and lay persons active in the Association and its affiliates will gather to assist local associations in program development will be held this Spring. One full day of each meeting will be devoted to discussion of the rheumatic fever prevention program. Emphasis will be placed on participation of physicians in these discussions. The schedule of meetings follows:

Southern Region, March 30–31, Andrew Jackson Hotel, Nashville, Tenn.
New England and New York Region, April 6–7, Northfield Hotel, East Northfield, Mass.
Middle Atlantic Region, April 13–14, Lord Baltimore Hotel, Baltimore.
North Central Region, April 20–21, Leland Hotel, Aurora, Ill.
West Central Region, May 11–12, Town House, Kansas City, Kan.
Pacific and Rocky Mountain Region, May 19–20, Hotel Mar Monte, Santa Barbara, Calif.

CARTOON FILM SEEKS TO DISPEL HEART DISEASE MISCONCEPTIONS

Popular misconceptions and exaggerated fears about heart attacks and heart disease so often encountered by physicians are dispelled through the medium of an animated color cartoon, "Pump Trouble" now being distributed by the Association.

"Pump Trouble" employs the blend of humor, art and music which has won wide recognition for its producers, UPA (United Productions of America). The 13½-minute color cartoon, made for the Association, features as its central figure, Cordell Pump, whose overactive imagination convinces him he is the victim of a heart attack. He is prepared to resign himself to invalidism or worse until his doctor clears up his false notions.

CARDIOVASCULAR RESEARCH TRAINING PROGRAM TO BE HELD AT GEORGIA

A postgraduate cardiovascular research and training program, jointly supported by the American Heart Association and the National Heart Institute of the U. S. Public Health Service, will be conducted at the Departments of Physiology and Pharmacology, Medical College of Georgia, Augusta, Ga., starting on July 1. A stipend of $3,400 plus $350 for each dependent and certain expenses will be provided to participants. Inquiries and requests for application forms should be addressed to either of the directors of the program, Dr. W. F. Hamilton or Dr. R. P. Ahlquist, Medical College of Georgia, Augusta, Ga.

CONFERENCE ON PUBLIC HEALTH ASPECTS OF PEDIATRIC CARDIOLOGY

The Seventh Conference on "The Public Health Aspects of Rheumatic Fever and Pediatric Cardiology" conducted by the Department of Pediatrics of the Grace-New Haven Community Hospital will be held from March 28 through April 7.

Physicians, nurses, medical social workers and all others concerned with carrying forth state or local rheumatic fever programs are invited to attend the conference.

Requests for additional information or applications for attendance should be addressed to Ruth Whittemore, M.D., Director, New Haven Rheumatic Fever and Cardiac Program, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.

GORDON RESEARCH CONFERENCE ON BLOOD, JUNE 13–17

The Gordon Research Conference on Blood, named in honor of Neil E. Gordon, will be held at the Kimball Union Academy, Meriden, New Hampshire, June 13–17. This is the first conference on blood to be held in a series of scientific meetings initiated in 1931. The conference will be devoted to informal presentations and exchanged of information on current and proposed research programs. Among the topics to be treated is *Blood Lipids—Their Form, Stability and Fate*. Those interested in contributing papers and in participating may secure full information from Herbert L. Davis, Ph.D., Department of Biochemistry, Univer-

sity of Nebraska College of Medicine, Omaha 5, Nebraska.

MEETINGS CALENDAR

March 17–19: International Symposium on Cardiovascular Surgery, Henry Ford Hospital, Detroit, Mich. Dr. Conrad R. Lam, 2799 West Grand Boulevard, Detroit 2.

March 20–23: Aero Medical Association 26th Annual Meeting, Washington, D.C. Lt. Col. J. B. Sweeney, Office of the Surgeon General USAF, Washington 25, D.C.

April 5: Second Microcirculatory Conference for Physiology and Pathology sponsored by the American Association of Anatomists, Benjamin Franklin Hotel, Philadelphia.

April 10–16: American Society of Experimental Pathology, San Francisco. Cyrus C. Erickson, 847 Union Avenue, Memphis 3.

April 10–16: American Society for Pharmacology & Experimental Therapeutics, San Francisco. Carl C. Pfeiffer, 1853 W. Polk Street, Chicago 12.

April 23–29: Industrial Medical Association, Buffalo, N. Y. H. Glenn Gardiner, Inland Steel Co., East Chicago, Ind.

April 24–29: Inter-American Congress of Radiology, Shoreham Hotel, Washington, D.C. Dr. Eugene P. Pendergrass 3400 Spruce Street, Philadelphia 4.

April 27–29: American Surgical Association, Philadelphia. R. Kennedy Gilchrist, 59 East Madison Street, Chicago 3.

May 1: American Federation for Clinical Research, Atlantic City, N. J. Dr. William H. Beierwaltes, University Hospital, Ann Arbor, Mich.

May 2: American Society for Clinical Investigation, Atlantic City, N. J. J. D. Meyers, 622 West 168th Street, New York 32.

May 3–4: Association of American Physicians, Atlantic City, N. J. W. Barry Wood, Jr., 600 S. Kingshighway Blvd., St. Louis.

May 6–8: Student American Medical Association, Chicago. Russell F. Staudacher, 510 N. Dearborn Street, Chicago 10.

May 8–13: Society of American Bacteriologists, New York. J. H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, New York.

May 23–27: National Tuberculosis Association, Milwaukee. Mrs. Morrell DeReign, 1790 Broadway, New York 19.

May 1955: American Society of Neurological Surgeons, Chicago. Bronson S. Ray, 525 E. 68th Street, New York 21.

June 3–4: American Rheumatism Association, Hotel Dennis, Atlantic City. W. H. Kammerer, 33 East 61 Street, New York 21.

June 5: Society for Vascular Surgery, Atlantic City, N. J. George D. Lilly, 25 S.E. Second Ave., Miami 32.

June 6–10: American Medical Association Annual Meeting, Atlantic City. Dr. George F. Lull, 535 N. Dearborn Street, Chicago 10.

June: American Rheumatism Association, Atlantic City, N. J. W. H. Kammerer, 33 E. 61st Street, New York 21.

ABROAD

April 1–5: Japan Medical Congress, Kyoto University and Kyoto Prefectural Medical College, Kyoto. Dr. Mitsuhary Goto, University Hospital, Medical Faculty of Kyoto University, Kyoto, Japan.

April 10–18: International Congress of Urology, Athens. Dr. Z. Kaires, 25 rue Voukourestion, Athens, Greece.

May 23–26: International Surgical Congress, Geneva, Switzerland. Dr. Max Thorek, 15 6 Lake Shore Drive, Chicago, Ill.

May 26–31: International Congress of Comparative Pathology. Lausanne. Professor Hauduroy, 9 rue Cesar Roux, Lausanne, Switzerland.

AHA AWARD WINNERS

Following is a complete list of Career Investigators, Established Investigators and Fellows selected by the Research Committee of the Association:

Career Investigators

Lorber, Victor, University of Minnesota Medical School, Minneapolis.

Pappenheimer, John, Harvard Medical School, Boston.

Coons, Albert H., Harvard Medical School, Boston.

Continued Established Investigators

Aikawa, Jerry Kazuo, immunophysiology, University of Colorado School of Medicine, Denver.

Cavert, Henry Mead, metabolism and permeability of heart tissue investigated with isotopic techniques, University of Minnesota Medical School, Minneapolis.

Cohn, Mildred, mechanisms of phosphorylation and phosphate transfer reactions, Washington University School of Medicine, St. Louis.

Conn, Hadley L., Jr., a study of the alterations in pressure-volume-flow relationships within the cardiovascular system produced by direct cardiovascular stresses; and the effect of these alterations on transcapillary kinetics and organ metabolism, University of Pennsylvania Medical School, Philadelphia.

Curran, George Lally, the metabolic aspects of cardiovascular disease with particular reference to lipid metabolism, University of Kansas Medical Center, Kansas City.

Orell, William, biochemical studies of the sympathetic nervous system in relation to cardiovascular function, University of California School of Medicine, Los Angeles.

Eckstein, Richard W., the coronary collateral circulation; the oxygen consumption of the right ventricle, Western Reserve University School of Medicine, Cleveland.

Edelman, Isidore Samuel, body water and electrolytes studied with tracers, University of California School of Medicine, San Francisco.

Elkinton, J. Russell, cardiovascular physiology, University of Pennsylvania School of Medicine, Philadelphia.

Fishman, Alfred P., cardiodynamic and renal interplay in the production of congestive heart failure, Columbia University College of Physicians and Surgeons, New York.

Gaudino, Mario, studies on the intra and extracellular distribution of water and electrolytes in the organism as a whole and in tissues by means of radio-active indicators, New York University College of Medicine, New York.

Gergely, John, energetics and contractile proteins of heart muscle, Massachusetts General Hospital, Boston.

Goodall, McChesney, (a) effect of cervico-stellate ganglionectomy on the adrenaline and noradrenaline content of sheep heart. (b) unknown sympatholytic factor present in mammalian heart, Duke University School of Medicine, Durham, N. C.

Goodyer, Allan V. N., hemodynamic factors affecting electrolyte metabolism and the renal excretion of electrolytes, Yale University School of Medicine, New Haven.

Grisolia, Santiago, enzymatic patterns of nitrogen metabolism in heart muscle, University of Kansas Medical School, Kansas City.

Kaplan, Melvin H., attempt to localize tissue-deposited streptococcal antigens and antibodies in animal and human tissues by means of the fluorescein-labeling technique; possible application to study of the pathogenesis of cardiac and skin lesions in rheumatic fever, House of the Good Samaritan and Children's Medical Center, Boston.

Lepeschkin, Eugene, electro-physiological interpretation of the normal and pathological ventricular complex of the electrocardiogram, University of Vermont, Burlington.

Mann, George V., the cause and prevention of atherosclerosis, Harvard School of Public Health, Boston.

Materer, Frank M., (1) cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technique; (2) ballistocardiographic studies in the normal and abnormal subject, University of Pittsburgh School of Medicine, Pittsburgh.

Mathews, Martin B., the physical chemistry of the acid mucopolysaccharides of connective tissue and their protein complexes, University of Chicago, Chicago.

Metcalfe, James, changes in the maternal circulation during pregnancy and labor. Boston Lying-in Hospital, Boston.

Mommaerts, Wilfried, F. H. M., biochemistry of muscular contraction, Western Reserve University School of Medicine, Cleveland.

Osborn, John J., extra-corporeal circulation, physiology of hypothermia, and intra-cellular fluid and ionic shifts during respiratory acidosis, Stanford University School of Medicine, San Francisco.

Peterson, Lysle Henry, volume pressure, 'distensibility' of intact veins, arterial circulation with view to calculating stroke volume, integration of peripheral c-v-reflexes. University of Pennsylvania Medical School, Philadelphia.

Rose, John C., (1) studies of the circulation in the dog using a mechanical left ventricle; (2) a sonic flowmeter; (3) studies in aortic insufficiency; (4) studies on the relationship between arterial pressure and cardiac auscultatory phenomena, Georgetown University Medical Center, Washington, D. C.

Sanadi, D. Rao, studies on (a) oxidative phosphorylation and (b) amino acid metabolism, University of California Medical School, Los Angeles.

Schmidt-Nielsen, Bodil M., comparative kidney physiology, Duke University School of Medicine, Durham, N. C.

Singer, Thomas P., studies on oxidative metabolism of sulfur amino acids in animals; studies on metabolism and function of new coenzymes, Edsel B. Ford Institute for Medical Research, Henry Ford Hospital, Detroit.

Sprinson, David B., (a) biochemistry of one-carbon intermediates; (b) biosynthesis of aromatic compounds in bacteria, Columbia University College of Physicians and Surgeons, New York.

Stamler, Jeremiah, experimental atherosclerosis; experimental hypertension, renal function in edema formation, Michael Reese Hospital, Chicago.

Stavitsky, Abram B., studies on the basic mechanisms of antibody production *in vivo* and *in vitro*, Western Reserve University School of Medicine, Cleveland.

Stefanini, Mario, establishment of 'profile' of tests for diagnosis of thrombotic tendency; relation of the endocrine system to the blood coagulation mechanism and the pathogenesis of thromboembolism; possibilities of employment of fibrinolysin in the treatment of thromboembolism, St. Elizabeth's Hospital, Boston.

Stetson, Chandler A., investigations in rheumatic fever, New York University College of Medicine, New York.

Tobian, Louis, Jr., the relation of steroids and sodium to hypertension; the role of steroids and sodium to hypertension; the role of steroid intoxication in toxemia of pregnancy; the role of emulsifying forces in plasma in pregnancy; the role of emulsifying

forces in plasma in atherosclerosis, University of Minnesota School of Medicine, Minneapolis.

Wessler, Stanford, the pathogenesis of intravascular thrombosis, Beth Israel Hospital, Boston.

New Established Investigators

Abelmann, Walter H., the circulation in disorders of metabolism and the regulatory role of the liver, The Thorndike Memorial Laboratory, Boston City Hospital and Department of Medicine, Harvard Medical School, Boston.

Barker, Earl Stephens, studies in renal physiology—normal and pathologic, University of Pennsylvania, Renal Study Section, Philadelphia.

Beck, William Samson, the mechanism by which hydrogen made available by carbohydrate oxidation is utilized for fatty acid synthesis, New York University College of Medicine, New York.

Briller, Stanley Arthur, energetics of the myocardium, New York University College of Medicine, New York.

Brodsky, William Aaron, renal and electrolyte metabolism, University of Louisville School of Medicine, Louisville.

DuBois, Arthur Brooks, gas exchange in the lungs, mechanics of breathing, and pulmonary capillary blood flow, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

Farber, Saul J., the role of electrolytes and their relationship to extracellular and intracellular organic constituents in heart disease and other diseases producing edema, New York University College of Medicine, New York.

Goldthwait, David Atwater, the biosynthesis of purine nucleotides, Western Reserve University School of Medicine, Cleveland.

Leaf, Alexander, a study of the factors which regulate fluid and electrolyte balance, Massachusetts General Hospital, Boston.

Mackler, Bruce, studies on the metabolic sequences involved in electron transport in mammalian tissues, Institute for Enzyme Research, University of Wisconsin, Madison.

Paterson, Philip Young, pathogenesis of selected forms of tissue damage, University of Virginia School of Medicine, Charlottesville, Va.

Szent-Gyorgyi, Andrew Gabriel, studies on the structure of myosin, Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Mass.

Zweifach, Benjamin William, biochemical analysis of structural elements of blood-tissue barrier, Laboratory of Cellular Physiology, New York University, New York.

New Research Fellowships

Anderson, George Spaulding, studies on the visceral circulation in patients with various types of acquired and congenital heart disease, under J. W. Culbertson, State University of Iowa Hospitals, Iowa City.

Ballon, Jonathan Daniel, studies in pulmonary embolism, under Stanford Wessler, Beth Israel Hospital, Boston.

Boucot, Nancy George, fluid and electrolyte balance with pulmonary and renal emphasis, under John P. Merrill, Peter Bent Brigham Hospital, Boston.

Bronner, Felix, mechanisms of calcification, with special reference to the role of chondroitin sulfate, under T. M. Rivers, The Rockefeller Institute for Medical Research, New York.

Brown, James Lawrence, role of adrenergic amines in cardiovascular disease, under Ralph Eugene Smith, C-V Laboratory, Veterans Administration Hospital, University of Minnesota, Minneapolis.

Burack, Walter Richard, mechanism of action of induced hypothyroidism when it alleviates symptoms in angina pectoris and congestive heart failure, under Herrman Blumgart, Beth Israel Hospital, Boston.

Chao, Fu-Chuan, a study of nucleoproteins in yeast, chick embryo and mammalian tissues, under J. Murray Luck, Stanford University, San Francisco.

Cominsky, Burton, hemodynamics of the splanchnic vascular bed, under Stanley E. Bradley, Columbia University College of Physicians and Surgeons, New York.

Corcoran, John William, the biosynthesis of porphyrins, under David Shemin, Columbia University College of Physicians and Surgeons, New York.

Damon, Albert, constitutional factors in health, occupation, and disease, under William H. Sheldon, Columbia-Presbyterian Medical Center, New York.

Davidson, Douglas George, effect of clamping renal artery on Na+ clearance, under Robert W. Berliner, National Institutes of Health, Bethesda, Md.

Dickerman, Herbert William, mechanisms of biological oxidations and phosphorylations in isolated metochondria and in extracts and enzymes derived from metochondria, under Albert Lehninger, Johns Hopkins School of Medicine, Baltimore.

Finnerty, Frank A., Jr., (1) investigations on toxemia of pregnancy; (2) studies on the cerebral and cardiac hemodynamics in postural hypotension; (3) cerebral and cardiovascular studies during hypotensive and freezing "anesthesia", under Hugh H. Hussey, Georgetown Medical Division, District of Columbia General Hospital, Washington, D. C.

Frazier, Howard Stanley, the effect of ouabain on the potassium transport of the normal and failing myocardium of the frog, under Arthur K. Solomon, Harvard Medical School, Boston.

Gonzalez, I. Ernest, the influence of steroid hormones on the histochemistry of the vascular bed and its response to injury—a study in atherogenesis, under Robert H. Furman, Oklahoma Medical Research Foundation, Oklahoma City.

Gordon, David Buddy, an experimental study of malignant hypertension, under G. W. Pickering, Medical Unit, St. Mary's Hospital, London, England.

G rdon, Gerald S., study of cardiac metabolism, under J. D. Myers, Duke University Hospital, Durham, N. C.

H tch, Frederick Tasker, biochemical aspect of a degenerative disease of man, under Irwin W. Sizer, Massachusetts Institute of Technology, Cambridge, Mass.

H ath, Edward Charles, function of the direct oxidative pathway for glucose in the cell, under B. L. Horecker, Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

Hoshiko, Tom, the excretion of chloride by the perfused frog kidney, under Hans H. Ussing, Laboratory of Zoophysiology, University of Copenhagen, Denmark.

Huckabee, William Edward, effects of cardiovascular disease on oxidative and non-oxidative metabolism, under Robert W. Wilkins, Massachusetts Memorial Hospitals, Boston.

Killip, Thomas, 3rd, Cardio pulmonary function in obesity, under Daniel Lukas, New York Hospital, New York.

Knisely, William Hagerman, direct microscopic study of the responses of normal mammalian lung vasculature to various stimuli, under Eugene A. Stead, Jr. and Joseph Markee, Duke University School of Medicine, Durham, N. C.

Kuida, Hiroshi, measurement of regional blood volumes and flows; physiological studies during cardiac surgery and transbronchoscopic left heart catheterization, under Lewis Dexter, Peter Bent Brigham Hospital, Boston.

Kuo, Peter T., the study of the intravascular distribution of plasma lipoprotein particles as they are influenced by the flow dynamics, under Calvin F. Kay, University of Pennsylvania, Philadelphia.

Lamfrom, Hildegard, studies on the mechanism of experimental renal and human hypertension, under Jens Bing, Institute for General Pathology, University of Copenhagen, Denmark.

Lazzarini, Jr., Abel Alfred, studies of the metabolic and immunological changes occurring in transplanted tissues, under J. William Hinton, New York University-Bellevue Medical Center, New York.

M tthews, Edward Carshore, polarographic measurement of oxygen tension in infants and children, nder Samuel Kaplan, University of Cincinnati, Cincinnati.

N tell, Judith, the relation of potassium metabolism o acid-base balance, under Isidore S. Edelman, niversity of California School of Medicine at he San Francisco County Hospital, San Francisco.

N nninga, Luddo B., binding of ions to heavy and ght moromyosin and tomyosin binding of adenoine, adenine, ATP, ADP, etc. to the same proeins, under Albert Szent-Gyorgyi, Institute for luscle Research, Woods Hole, Mass.

S midt, Willard Carl, a study of the host response to streptococcal antigens and the localization of these antigens in host tissue: I. the type-specific M protein; II. the non-type-specific nucleoproteins, under Charles H. Rammelkamp, Cleveland City Hospital, Cleveland.

Sieker, Herbert Otto, the regulation of the circulation in small blood vessels, veins and pulmonary vessels in relation to the function of organ systems and tissue metabolism in normal and diseased states, under Eugene A. Stead, Jr., Duke University School of Medicine, Durham, N. C.

Shapiro, Bernard, the role of sulfhydryl compounds in the active transfer of substances across cell membranes, under J. Russell Elkinton, Hospital of the University of Pennsylvania, Philadelphia.

von Kaulla, Kurt Nikolai, the activity of the components of the fibrinolytic and clotting system in cardiovascular diseases with special consideration of the excretion of these components with the urine, under Gordon Meiklejohn, University of Colorado School of Medicine, Denver.

Weiss, Arthur J., investigation of the kinetics of the reactions between various components of the coagulation system, under L. M. Tocantins, Jefferson Hospital, Philadelphia.

Weissler, Arnold, Mervin, studies on liver circulation and metabolism, under Jack D. Myers, Duke University Hospital, Durham, N. C.

Renewal Research Fellowships

Brewster, William Russell, Jr., relationship of l-thyroxine to cardiovascular, calorigenic and metabolic effects of l-epinephrine and l-norepinephrine, under Dean A. Clark, Massachusetts General Hospital, Boston.

Camara, Augusto A., further studies of the problem of edema, including the mechanism by which corticotropin (ACTH) relieves resistant cardiac edema; and the nature of edema in beriberi and eclampsia with special reference to electrolyte metabolism and some endocrine factors, under Agerico B. M. Sison, College of Medicine, University of the Philippines, Manila.

Childs, Alfred Wheeler, the relation of anion loading to the distribution of delay of sodium excretion in man; the effect of refrigeration hypothermia on renal function, under Stanley E. Bradley, Columbia University College of Physicians & Surgeons, New York.

Done, Alan K., relationship of salicylates to pituitary-adrenal system and its secretions, under Vincent C. Kelley, University of Utah.

Dontas, Anastasius S., pharmacology of anti-hypertensive agents; electro-physiological investigation of prolonged altered circulatory homeostasis, under Cyrus C. Sturgis, University of Michigan Medical School, Ann Arbor.

Flavin, Jr., Martin, mechanism of action of B-keto thiolase of heart muscle; metabolism of propionic

acid in heart muscle, under Severo Ochoa, New York University Medical School, New York.

Friedman, Edward W., bacterial factor in traumatic shock, under Jacob Fine, Beth Israel Hospital, Boston.

Gibson, William, study of an external electric cardiac pacemaker in Stokes-Adams disease and circulatory arrest; pathology of the heart and its relation to the clinical manifestations of congestive failure, under Herrman L. Blumgart and Paul M. Zoll, Beth Israel Hospital, Boston.

Gunn, Chesterfield Garvin, Jr., the influence of C.N.S. mechanisms on the cardiovascular system and its disorders, under H. W. Magoun, University of California, Los Angeles.

Hackel, Donald Benjamin, myocardial metabolism studied by coronary venous catheterization in intact animals, under Thomas D. Kinney, Western Reserve University at City Hospital, Cleveland.

Hagans, James Albert, studies as to the role of the autonomic nervous system and possible humoral factors involved in the maintenance of vasomotor tone in certain disease states and during adrenal steroid therapy, under Eugene B. Ferris and Albert A. Brust, Emory University School of Medicine, Atlanta.

Jardetzky, Oleg, rates of synthesis and breakdown of high energy phosphates in the normal and failing mammalian heart, under Victor Lorber, University of Minnesota, Minneapolis.

Padawer, Jacques, the physiology of the mast cell and its relation to cardiovascular disease, under Albert S. Gordon, New York University Graduate School of Arts and Science, New York.

Porter, Richard, factors governing the distribution of acid among the extra- and intra-cellular spaces, under William B. Schwartz, New England Center Hospital, Boston.

Rapaport, Elliot, pulmonary red cell, plasma, and extracellular fluid volumes under conditions of varying circulatory stress.

Reiss, Oscar Kully, the mechanism of action of a hypocholesteremic factor isolated from brain, under Richard J. Jones, University of Chicago, Chicago.

Rudolph, Abraham Morris, the study of pulmonary hypertension in congenital heart disease, under Charles A. Janeway, Harvard Medical School, Boston.

Sharp, John Turner, hemodynamic studies in valvular heart disease, with particular reference to the brachial artery pulse pressure curve, under David G. Greene, University of Buffalo School of Medicine, Buffalo, N. Y.

Sheppard, Erwin, electrostatic forces involved in blood coagulation and the mode of action of ionic anticoagulants, under Irving S. Wright, New York Hospital-Cornell Medical Center, New York.

Spurr, Gerald Baxter, Cardiovascular adjustments to prolonged, profound hypothermia, under Steven M. Horvath, State University of Iowa, Iowa City.

Surawicz, Borys, studies of genesis and mechanism of the electrocardiographic patterns of electrolyte imbalance, under Samuel Bellet, Philadelphia General Hospital, Philadelphia.

Walker, W. Gordon, changes in plasma volume and capillary permeability in congestive heart failure, under A. M. Harvey and E. C. Andrus, Johns Hopkins University School of Medicine, Baltimore.

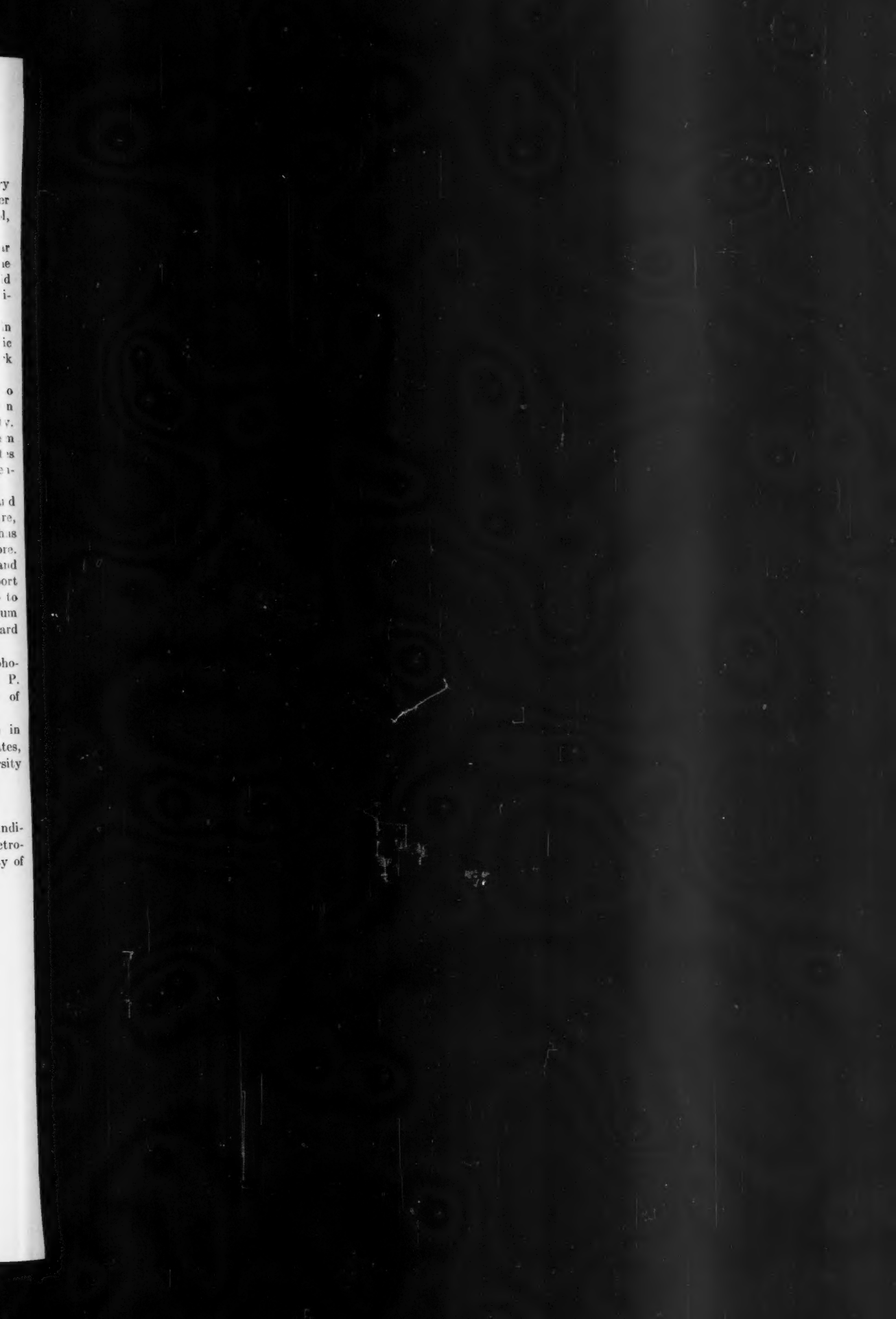
Walters, Donald Hermann, the effect of calcium and magnesium on the sodium and potassium transport in the human erythrocyte and its relationship to cardiac muscle physiology (i.e. calcium-magnesium antagonism), under A. K. Solomon, Harvard Medical School, Boston.

Weiss, Samuel Bernard, the synthesis of phospholipides in cell free systems, under Eugene P. Kennedy, Ben May Laboratory, University of Chicago, Chicago.

Wennesland, Reidar, studies of blood volume in healthy individuals and selected disease states, under Ellen Brown and J. Hopper, Jr., University of California Medical Center, San Francisco.

Continued Research Fellow

Nelson, Clifford V., the relationship between individual cardiac fiber response and the electrocardiogram, under Hans H. Hecht, University of Utah Medical School, Salt Lake City.



Circulation

MARCH 1955
VOL. XI NO. 3

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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